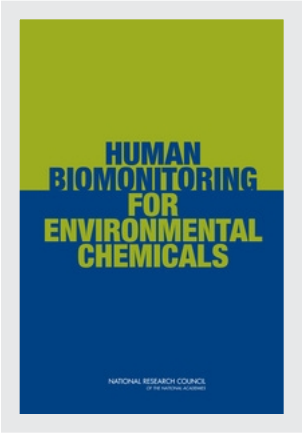

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DETAILS

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HUMAN BIOMONITORING FOR ENVIRONMENTAL CHEMICALS

Committee on Human Biomonitoring for Environmental Toxicants

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Biomonitoring has various applications; the focus in this report is on the role of biomonitoring as an exposure-assessment tool, which is central to public-health efforts. Repeatedly throughout recent history, biomonitoring data have helped to confirm health effects of environmental exposures and have validated public-health policies. Population-based biomonitoring studies have identified new chemicals found in the environment and in human tissues, monitored changes in exposures, and established the distribution of exposures among the general population. Biomonitoring data—when used in conjunction with available epidemiology, toxicology, and pharmacokinetic modeling data—can estimate how much of a chemical has been absorbed into the body and provide a measure of potential health risk. The ultimate objective of biomonitoring is to link information on exposures, susceptibility, and effects to understand the public health implications of exposure to environmental chemicals.

In spite of its potential, tremendous challenges surround the use of biomonitoring, and our ability to generate biomonitoring data has exceeded our ability to interpret what the data mean to public health. The challenges include improving the design of biomonitoring studies, interpreting what biomonitoring data mean, and understanding ethical and communication issues that are essential to the continued advancement of this field. To address the challenges, Congress asked the National Academies to assess key uncertainties related to the use and interpretation of biomonitoring data.

In this report, the Committee on Human Biomonitoring for Environmental Toxicants reviews current practices and makes recommendations for

improving the interpretation and uses of human biomonitoring data. The committee also develops a research agenda that addresses the key uncertainties in the field and provides guidance for collecting and interpreting biomonitoring data in the future.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report: Asa Bradman, University of California, Berkeley; Ludwine Casteleyn, Ministry of the Flemish Community; Harvey Clewell, CIIT Centers for Health Research; Kannan Krishnan, University of Montreal; Philip Landrigan, Mount Sinai School of Medicine; Michael Morgan, University of Washington; Joseph Rodricks, ENVIRON International Corporation; Kenneth Rothman, Harvard School of Public Health; Susan Santos, FOCUS Group; Paul Schulte, National Institute for Occupational Safety and Health; H. Catherine Skinner, Yale University; Karel Van Damme, University of Leuven; and Jean-Philippe Weber, Institut National de Santé Publique du Québec.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by the review coordinator Steven Tannenbaum, Massachusetts Institute of Technology, and the review monitor, Johanna Dwyer, Tufts University. Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the committee and the institution.

The committee gratefully acknowledges the following for making presentations and for providing information: Harold Zenick, U.S. Environmental Protection Agency; Larry Needham, Jim Pirkle, John Osterloh, Susan Schober, Thomas Sinks, and Edward Thompson, Centers for Disease Control and Prevention; Paul Schulte, National Institute for Occupational Safety and Health; Richard Jackson, University of California, Berkeley; James VanDerslice, Washington State Department of Health; Richard Becker, American Chemistry Council; Steven Robison, Procter and Gamble Company; Lauren DiSano, Association of Public Health Laboratories; Angelina

Duggan, CropLife America; Lorne Garretson, Environmental Defense; and Nancy Kass, Johns Hopkins Bloomberg School of Public Health.

The committee is also grateful for the assistance of the National Research Council staff in preparing this report. Staff members who contributed to this effort are Eileen Abt, project director; James Reisa, director of the Board on Environmental Studies and Toxicology; Jennifer Saunders, associate program officer; Norman Grossblatt, senior editor; Mirsada Karalic-Loncarevic, research associate; Lucy Fusco, program associate; Morgan Motto, senior project assistant; and Kemi Yai, project assistant.

I would especially like to thank the members of the committee for their efforts throughout the development of this report.

Thomas Burke, Chair
Committee on Human Biomonitoring for
Environmental Toxicants

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HUMAN BIOMONITORING FOR ENVIRONMENTAL CHEMICALS

Summary

Identifying, controlling, and preventing population exposures to potentially harmful environmental chemicals have been cornerstones of U.S. environmental health efforts. Biomonitoring has become a tool that is central to these efforts. Repeatedly, biomonitoring data have confirmed environmental exposures and validated public-health policies. For example, population data on blood lead concentrations associated with adverse health effects provided impetus for the U.S. Environmental Protection Agency's (EPA's) regulatory reduction of lead in gasoline. Blood lead concentrations declined in parallel with the resulting reduction. Methylmercury concentrations in blood and hair that correlated with adverse neurodevelopmental effects provided a rationale for EPA's revision of the oral reference dose.[1] Serum cotinine, a marker of exposure to secondhand smoke, in U.S. children and adults declined by more than 50% among nonsmokers from 1998 to 2002, indicating the effectiveness of smoking cessation efforts in the United States.

Biomonitoring is defined in this report as one method for assessing human exposure to chemicals by measuring the chemicals or their metabolites in human tissues or specimens, such as blood and urine. In studies conducted by the Centers for Disease Control and Prevention (CDC), biomonitoring data have helped to identify chemicals found in the environ-

[1]A reference dose is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

ment and in human tissues, to monitor changes in exposure, and to investigate the distribution of exposure among the general population. Biomonitoring provides a measurement of exposure that—when used with available epidemiologic, toxicologic, and pharmacokinetic modeling data—can be used to estimate how much of a chemical has been absorbed into the body and to provide an indicator of potential health risk. State and local officials can use biomonitoring data to help assess environmental risks to specific sites or populations. In occupational and clinical medicine, biomonitoring can be used as a surveillance tool to help interpret a clinical problem or to monitor an exposure trend. Biomonitoring, in short, is a versatile means of assessing exposure.

Many population-based biomonitoring efforts are taking place in the United States and in Europe. In the United States, CDC publishes periodic national reports on human exposure to environmental chemicals that detail the concentrations of chemicals and their breakdown products in blood and urine of a representative sample of the U.S. population. Other government organizations, including EPA and the National Institutes of Health (NIH), are conducting and sponsoring biomonitoring studies.

In spite of the potential value of biomonitoring, tremendous challenges surround its use. They include improving our ability to design biomonitoring studies, interpreting what biomonitoring data mean for public health, addressing ethical uses of the data, and communicating results to study participants, policy-makers, and the public.

The ability to generate new biomonitoring data often exceeds the ability to evaluate whether and how a chemical measured in an individual or population may cause a health risk or to evaluate its sources and pathways for exposure. As CDC states in its *National Reports on Human Exposure to Environmental Chemicals*, the presence of a chemical in a blood or urine specimen does not mean that the chemical causes a health risk or disease. The challenge for public-health officials is to understand the health implications of the biomonitoring data, to provide the public with appropriate information, and to craft appropriate public-health policy responses.

To address some of those challenges raised by biomonitoring data, Congress[2] directed EPA to ask the National Research Council (NRC) of the National Academies to perform an independent study.

CHARGE TO THE COMMITTEE

In response to the request, the NRC established the Committee on Human Biomonitoring for Environmental Toxicants, which prepared this

[2]In the conference report to accompany H.R. 2861, the Department of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriations Act, 2004.

report. The committee was charged to review current practices and recommend ways to improve the interpretation and uses of human biomonitoring data on environmental chemicals. It was asked to develop an overall research agenda for addressing the uncertainties in biomonitoring data, to improve evaluations and characterizations of health risks from biomonitoring data, and to improve tracking of changes in biomonitoring data potentially relevant to public health.

In undertaking its evaluation, the committee focused primarily on biomonitoring in population-based studies, such as CDC's *National Report on Human Exposures to Environmental Chemicals* and EPA's National Human Exposure Assessment Survey, because these studies raise the most far-reaching and challenging issues regarding the interpretation of biomonitoring data. The population-based studies have demonstrated that representative samples of the population have relatively low concentrations of chemicals in their bodies; [3] however, for most of these chemicals, the data and methods needed to interpret what the concentrations mean are often not available. The committee also considered applications of biomonitoring beyond the population-based studies—such as source investigations, occupational investigations, and individual risk characterization—since biomonitoring is used for myriad purposes.

THE COMMITTEE'S EVALUATION

Biomonitoring is a tool with great potential. It has been of value in identifying human exposures to chemicals that pose potential harm to human health, in understanding exposure status and trends, in fostering public-health interventions, and in validating environmental-health policies. Rapidly developing technological capabilities to measure chemicals in the human body have increased the availability of biomonitoring information. However, the complete potential of this tool has yet to be realized, inasmuch as the science (epidemiology, toxicology, pharmacokinetic modeling, and exposure assessment) needed to understand the implications of biomonitoring data for human health is still in its nascent stages. For some chemicals (such as mercury and lead), the health risks and effects are well known; but for most of the chemicals currently measured, the risks cannot be interpreted. Scientists, policy-makers, and the public are just beginning to grasp the tremendous ethical and communication challenges that the biomonitoring data are creating.

In this report, the committee presents a roadmap for addressing many of the unanswered questions. The roadmap begins with a framework for

[3] In the 1-part-per-billion (ppb) range or below for many commonly used chemicals or their breakdown products.

characterizing the properties of biomarkers of exposure[4] and understanding the potential uses of the data. The committee then describes scientific principles and practices to ensure the proper conduct of biomonitoring studies; the guidelines are essential to ensure valid collection of the biomonitoring data. The committee uses this framework to illustrate various options for interpreting biomonitoring data, which depend on the properties of specific biomarkers. Chemical-specific data are used to demonstrate the various interpretative options. Challenges in communicating results in light of the difficulty of interpreting the data are discussed. In the sections that follow, the committee presents its roadmap and the findings and recommendations in the research agenda that have evolved from the roadmap.

Framework for Characterizing Biomarkers and Uses of Biomonitoring Data

As the number of biomonitoring studies and the number of subjects and chemicals measured increases, there is a need for clarification of the appropriate uses and interpretation of biomonitoring data. The general public needs to know the meaning and limitations of the data, and public-health officials, who are often called on for interpretation of results, also need to be adequately informed.

In Chapter 3 of this report, the committee presents a systematic framework or matrix to characterize the properties of biomarkers as a means to inform scientists and the general public about biomarkers and their significance in biomonitoring studies. The framework generally summarizes what is known about a biomarker and indicates potential research gaps that need to be addressed to meet the requirements for some specific uses.

The framework is intended to crystallize scientific discussion of specific biomarker issues. The committee recommends that investigators undertaking biomonitoring studies use the framework for considering all biomarkers that they intend to use. The framework will serve as a guide for interpreting the studies, in setting priorities among research needs, and in communicating study objectives to various audiences.

Considerations in the Design of Biomonitoring Studies

The *National Report on Human Exposure to Environmental Chemicals*, produced by CDC, is based on a representative sample of the population and a large number of chemicals, and uses well-documented analytic techniques. However, not all biomonitoring studies are conducted with the

[4]A biomarker of exposure is a chemical, its metabolite, or the product of an interaction between a chemical or some target molecule or cell that is measured in humans.

same rigor as the CDC studies. In Chapter 4 of this report, the committee discusses scientific practices in biomonitoring (study design, conduct, and analysis). Issues of design include selecting biomarkers for the study, identifying the population to be sampled, developing the sampling strategy to address the study questions or objectives, and assessing communication and ethical considerations. Study conduct includes consideration of the appropriate tissue or specimen to use, collection of samples, transportation of samples to the laboratory for analysis, and banking of the samples for additional analysis. Epidemiologic and statistical analyses stem from the objectives of the study design.

The committee concludes that it is critical for biomarker researchers to adhere to appropriate statistical principles when sampling populations to ensure that the biomonitoring results are valid and representative of the sampled population. In addition, biomarker studies should collect detailed information on cofactors (for example, socioeconomic status and lifestyle factors) to facilitate interpreting the data—an inconsistent practice at present. Laboratory analysis of human samples for trace concentrations of chemicals inevitably introduces some deviation from the true concentration into the sample results; federal agencies, such as CDC and the National Institute for Standards and Technology, and statutes, such as the Clinical Laboratory Improvement Act, could play important roles in improving the overall quality of biomonitoring data and their utility for health-related applications. Incorporating communication in the design of a biomonitoring study is essential to ensure easier communication at the end of the study and may make the technical aspects of the study proceed more smoothly. To that end, the committee recommends that biomonitoring program sponsors require planning for communication and evaluation in any application for funding.

Interpreting Biomonitoring Data

Considerable controversy often surrounds the interpretation of biomonitoring data. Researchers are generating biomonitoring data whose relevance to human health is unclear in many cases. For example, news-media reports present stories of people who have had their blood tested and are alarmed to learn that it contains hundreds of chemicals. For a number of those chemicals, scientific data could enable interpretation of individual measurements in comparison with validated reference values, but usually the interpretation stops with the mere observation that the chemical is present.

Biomonitoring data may be interpreted through either descriptive or risk-based approaches. The descriptive approaches present a statistical review of the data (for example, 10th, 25th, 50th, 75th, and 90th percentiles) to relate a given population to a comparable or reference population. Risk-based approaches are much more data-intensive and may use toxico-

logic, epidemiologic, or pharmacokinetic modeling data to relate biomonitoring data to other measures of toxicity in an effort to evaluate the risk associated with the amount of chemical in the body. Risk-based approaches potentially can provide better information on the health effects related to the biomonitoring data. However, for most chemicals that are capable of being measured in the human body, the available data are insufficient to assess risks based on measured concentrations. Because some of the interpretative approaches involve modeling and extrapolation, there are additional uncertainties and limitations in assessing the biomonitoring results. Understanding the uncertainties and limitations is important both for providing full disclosure regarding the reliability and credibility of the biomonitoring results and for defining data gaps and research needs.

Several risk-based approaches may be used, depending on the data available. The strongest approach, biomonitoring-based risk assessment, relies on biomarker-response relationships established in epidemiologic studies. Few chemicals are in that data-rich category (lead and mercury are two). Risk assessments that combine data from animal toxicology and human-exposure assessment studies can also be used to interpret biomonitoring data; the biomonitoring results may be interpreted within the context of the results of the risk assessment. Interpretations of chemical exposures that have used that approach include the herbicide glyphosate and the insecticide permethrin. For most other chemicals, however, there are no epidemiologic data on the relationship between the biomarker and the effect, and the exposure sources and routes are not known. Therefore, interpretation of the biomonitoring data is not possible via traditional risk assessment approaches, and an alternative risk-based approach, biomonitoring-led risk assessment, is used. In this case, pharmacokinetic modeling techniques are applied to convert the biomonitoring data into a format that can be used as exposure information in risk assessments. The specific approaches that may be used depend on the properties of each chemical and on the data available. Chemicals that have been subjected to biomonitoring-led risk assessment include dioxin, chlorpyrifos, perfluorooctanoic acid (PFOA), and phthalates.

The committee concludes that descriptive approaches are often important in laying a foundation on which risk-based approaches can build. The interpretative power of risk-based approaches varies widely, depending on the information available. To improve the interpretation of biomonitoring results, an expansion of the scientific database on many chemicals is needed.

Communicating Results from Biomonitoring Studies

Communicating biomonitoring results may be the most vexing challenge to the field of biomonitoring. Communication is essential to proper

interpretation and use of biomonitoring data, and it is intimately intertwined with and as important as technical aspects of biomonitoring. There is no one recipe for good biomonitoring communications, which will vary by study goals, the population sampled, biomarkers selected, exposures and health effects assessed, and audiences. If done properly, communication can assist experts to reach consensus on the meaning of biomonitoring results and help institutional and individual decision-makers determine appropriate courses of action.

To achieve proper communication requires explicit funding, early planning, and empirical evaluation of communication methods and messages. Perhaps most critically, early planning must assess the needs of the various audiences for biomonitoring information, and the study must be designed to meet those needs if feasible. Achieving these goals might entail pursuing partnerships with one or more audiences on project design, implementation, or interpretation and communication. Only rarely will communication with constituencies be one-way only (for example, scientists to public or policy-makers).

In Chapter 6, the committee presents several practical and research recommendations to address communication challenges. Practical measures include use of consistent terminology and concepts, expanded biomonitoring education for constituencies, communication training, and public documentation of methods to reduce exposures contributing to biomarkers of concern. Research measures include identifying how experts and nonexperts think about exposure and health effects, assessing current biomonitoring communication methods and impacts, identifying communication issues with respect to uncertainties in biomonitoring studies, and identifying beliefs and attitudes about exposure reduction and risk managers.

Given the central role of communication in the interpretation and use of biomonitoring data and the great uncertainty about what makes communication effective, building infrastructure and research in this field must have high priority for biomonitoring investigators and sponsors.

RESEARCH AGENDA

To realize the potential of biomonitoring, investment in research is needed to address the critical knowledge gaps that hinder the ability to use biomonitoring data and interpret what they mean with respect to risks to public health. The committee's research recommendations focus not on specific chemicals but rather on methods that can be applied to a broad array of chemicals. Implementation of the research recommendations by federal and state agencies and universities will benefit from an improvement in some parts of our nation's research infrastructure.

Research Recommendations

To address the challenge of improving the interpretation and use of biomonitoring data, the committee has developed four major findings and corresponding research recommendations. They will require a broader vision of biomonitoring—one that integrates a scientific approach for setting priorities among biomarkers for development; supports the epidemiology, toxicology, and exposure-assessment science required to interpret biomonitoring data; develops strategies for advancing the reporting of biomonitoring results; and strengthens understanding of the ethical issues that constrain the advancement of this field.

Finding: There has not been a coordinated and consistent public-health-based strategy for selecting how chemicals are included in or excluded from biomonitoring studies. There is a need for a consistent rationale for selecting chemicals for study based on exposure and public-health concerns.

Recommendation: Develop a coordinated strategy for biomarker development and population biomonitoring based on the potential for population exposure and public-health concerns.

Biomonitoring offers great promise as an effective technique for identifying chemicals and exposures of potential public-health significance. The committee finds that broad population screening for a large number of chemical biomarkers has provided valuable and, at times, surprising evidence of human exposure. That type of screening should continue. However, it can be improved. Most current biomonitoring relies on biomarkers that are generated through a variety of research avenues (such as epidemiology, analytic chemistry, and workplace monitoring), but the uncoordinated fashion in which such biomonitoring has occurred has allowed widespread exposures to go undetected—for example, polybrominated diphenyl ethers and PFOA. In addition, susceptible subpopulations, including infants and children, are generally omitted from large-scale biomonitoring studies because of difficulty in sample collection.

The committee recommends that a coordinated scientific strategy be developed to ensure that the selection of chemicals and the development of biomarkers focus first and foremost on the potential of chemicals to cause harm and consider the likelihood of substantial or widespread population exposure, including exposure of susceptible subpopulations. The biomonitoring strategy needs to set priorities among chemicals on the basis of one or more of the following: evidence of substantial or widespread exposure of the general population, biomonitoring data or exposure-analysis information that indicates exposure of susceptible subpopulations, toxicologic data

indicating that a chemical is capable of causing effects of public-health significance, and environmental persistence or use-pattern information that indicates that exposure will probably persist or increase in the future.

Developing the coordinated scientific strategy will require input from various agencies involved in biomonitoring and supporting disciplines, including CDC, EPA, and NIH (especially the National Institute of Environmental Health Sciences, and the National Toxicology Program), as well as the Food and Drug Administration and the U.S. Department of Agriculture. The coordinated input from those agencies would ensure that population-based biomonitoring studies would target chemicals of public-health concern as well as chemicals that are prudent to monitor because of exposure considerations. The scientific strategy would need to be transparent and well explained. Such a coordinated approach might reduce redundancies in research efforts among agencies and help to leverage funds for the most pressing public-health questions.

Finding: The ability to detect chemicals has outpaced the ability to interpret health risks. Epidemiologic, toxicologic, and exposure-assessment studies have not adequately incorporated biomonitoring data for interpretation of health risks at the individual, community, and population levels.

Recommendation: Develop biomonitoring-based epidemiologic, toxicologic, and exposure-assessment investigations and public-health surveillance to interpret the risks posed by low-level exposure to environmental chemicals. Where possible, enhance existing exposure-assessment, epidemiologic, and toxicologic studies with biomonitoring to improve the interpretation of results of such studies.

To better interpret biomonitoring data in the context of the committee's framework and to understand the public-health implications of the data, the committee offers a number of research recommendations in epidemiology, toxicology, pharmacokinetics, and exposure assessment. Development of biomarkers in epidemiology is needed to improve understanding of the relationships between biomonitoring data and health effects. Such development includes increasing the number of biosamples collected and stored in epidemiologic studies to provide future research opportunities for assessing associations between biomarkers and outcomes in existing study designs. Likewise, animal toxicologic-study designs need to include the collection of relevant biomarker data to facilitate development of biomarker-response relationships for the purpose of extrapolating biomonitoring results to humans. NTP toxicologic protocols serve as a relevant example. The committee also recommends the development of pharmacokinetic models to help

assess the influence of such factors as metabolism and sampling time that are critical to interpretation of the biomonitoring data. To understand the sources of exposure better, when interpreting the biomonitoring data, exposure assessment should be a component of population-based biomonitoring studies. Specifically, in large-scale biomonitoring studies, the committee recommends inclusion of a detailed and accurate exposure analysis for a subset of the population. It should include information on environmental media that are relevant to the specific chemical exposure pathways.

Finding: Effective communication of results is among the biggest challenges to the future of biomonitoring. Without appropriate strategies for understanding communication issues in the design, implementation, and evaluation of biomonitoring studies, the power to interpret and use the resulting data effectively is hampered.

Recommendation: Advance individual, community, and population-based strategies for reporting results of biomonitoring studies.

Given the central role of communication in interpreting and using biomonitoring data, research on public communication must have high priority for investigators and sponsors. To that end, the committee recommends research on how scientists and nonscientists understand causal links between external dose, internal dose, and biologic effects. In addition, assessing the content of current biomonitoring education and communication materials will help to evaluate their efficacy and determine the extent to which beliefs about causal linkages are accurately addressed in them.

Finding: Biomonitoring research presents a number of ethical issues about informed consent and the interpretation of results. For example, biomonitoring research is conducted with anonymized samples that limit the communication of results and potential follow-up with study subjects.

Recommendation: There is a need for review of the bioethical issues confronting the future of biomonitoring, including confidentiality, informed consent, reporting of results, and public-health or clinical followup.

Participants in public-health studies that measure hundreds of biomarkers might give "informed consent" only with respect to the general objectives of the study on the grounds that detailed discussion of each biomarker is not feasible. However, failing to provide more detailed information raises ethical questions. The committee recommends research

to identify methods to ethically and practically inform subjects who are participating in biomonitoring studies that measure hundreds of chemicals in a single person. In addition, the committee recommends the development of new approaches for obtaining blanket consent for future uses of biomonitoring data, inasmuch as controversy surrounding this issue has led to increased difficulty in obtaining approval for some biomonitoring studies.

Infrastructure Needs to Implement Research Agenda

The current scientific infrastructure to support the committee's research recommendations is severely limited. Improvements in research-related infrastructure are needed to support these recommendations and to enhance the value of biomonitoring activities. The infrastructure needs encompass enhancing laboratory capabilities, expanding the scope and utility of CDC's National Health and Nutrition Examination Survey (NHANES) data, maximizing the use of collected human samples, and fostering international biomonitoring collaboration. Many of these recommendations for infrastructure improvement are cost-effective because they rely on expansion of structures and activities that are already in place.

Targeted investments in federal, state, and university laboratories are needed to create the national capacity to use biomonitoring fully as a public-health tool. Analysis of human specimens for trace concentrations of environmental chemicals poses serious challenges to analytic chemistry. The growth in biomonitoring has provided for a new generation of more sensitive and selective instruments for chemical analysis; however, the costs associated with that equipment and the specialized skills required to perform the analyses have limited the number of laboratories capable of conducting the measurements. In recognition of the national deficiencies in laboratory capacity, CDC funded 33 states to identify local public-health problems and to develop plans to create the biomonitoring-laboratory capacity needed to address them; however, financial constraints limited the number of grants and the total amount of funding that was ultimately awarded. The committee recommends that CDC emphasize support of state public-health laboratories. In addition, improvements in laboratory methods are needed, including improved quality of laboratory data, better analytic sensitivity, ability to measure a greater number of chemicals reliably, and development of analytic methods that use more readily obtainable specimens (such as saliva, exhaled breath, and breast milk). The need for high-throughput, low-cost testing procedures will be increasingly apparent as biomonitoring techniques are more widely applied to large-scale epidemiologic studies and mass-casualty events, such as chemical terrorism or chemical accidents.

CDC's *National Reports on Human Exposure to Environmental Chemicals* provide the most comprehensive summary of biomonitoring data on a representative sample of the U.S. population. The committee supports CDC's efforts but argues for an expansion of the biomonitoring program and for procedural changes that would enhance the data's utility. The committee recognizes that in some cases CDC may not be able to undertake such efforts but that other organizations may be more appropriate. The committee concludes that additional data are needed on some ethnic groups, specific locations, and the young (infants, toddlers, and preschoolers). CDC should report additional data in the printed version of the national exposure reports, such as results below the 50th percentile, and ensure that the publicly available database is sortable by sample type, chemical, location, and socioeconomic characteristics.

Because of the scientific and cost-effective value of specimen banks for maintaining samples for future analyses, the committee concludes that there should be provisions for increased availability of previously collected and characterized samples. In addition, long-term funding for both existing and new biorepositories should be supported.

Biomonitoring is conducted on an international level by numerous organizations, and there is much knowledge to be gained from understanding patterns of exposure worldwide. The committee encourages the global exchange of biomonitoring information and expertise, including sharing of data, study approaches, and tracking of trends. To that end, the committee encourages the development of such information exchanges between EPA and the Organisation for Economic Co-operation and Development (OECD).

CONCLUSION

Advances in biomonitoring have provided a potentially powerful new lens for examining public exposures to toxic chemicals. However, the full promise of this tool for improving the nation's public health is still far from being realized. Unprecedented analytic sensitivity has brought new insights and new challenges. Population-based biomonitoring studies provide potentially valuable data for researchers, public-health officials, and the public for identifying human exposures, understanding trends, fostering public-health interventions, and validating environmental-health policies. However, the tool has underscored the critical need to address methodologic, ethical, and communication challenges.

This report presents a roadmap for approaching those challenges. It provides an overview of the state of the science, a profile of international applications, and guidance for the design of biomonitoring studies. It also presents a systematic approach to interpreting the public-health implica-

tions of biomonitoring results and communicating findings to the public. In its final chapter, the committee presents a research agenda that incorporates an integrated approach for setting priorities among biomarkers for development; supports the epidemiologic, toxicologic, and exposure-assessment science required to interpret biomonitoring data; and fosters the ethical and communication research required to convey study results effectively.

1

Introduction

Data from biomonitoring studies are becoming widely available and are increasingly used to understand the presence of chemicals in the human body and their effects on human health. At the same time, scientists, public-health officials, and the public have questions about the quality and scope of the available data, what the data tell us about potential risks to human health, and how future research can address these questions. Responding to a congressional request, the National Research Council established the Committee on Human Biomonitoring for Environmental Toxicants to review current practices in and recommend ways to improve the interpretation and uses of human biomonitoring for environmental toxicants.

This report defines biomonitoring as one method for assessing human exposure to chemicals by measuring the chemicals[1] or their metabolites[2] in human specimens, such as blood or urine (CDC 2005). A biologic indicator of exposure, or "biomarker" is a chemical, its metabolites, or the product of an interaction between the chemical and a target molecule or cell that is measured in an organism (WHO 2001; Metcalf and Orloff 2004).

[1]*Chemical*, used in the context of this report, refers to a chemical compound or element present in air, water, food, soil, dust, or other environmental medium (such as consumer products) (CDC 2003).

[2]A *metabolite* is a chemical alteration, produced by body tissues, of the original compound (CDC 2005).

BACKGROUND

Although biomonitoring has been used in the occupational-health arena since the 1890s to monitor exposure to lead (Sexton et al. 2004), it has recently become more widely used for many applications. Biomonitoring has tremendous utility, providing an efficient and cost-effective means of measuring exposure. Biomonitoring data—when used in conjunction with available epidemiology, toxicology, or pharmacokinetic modeling[3] data—can estimate a dose to assess how much has been absorbed into the body and can provide a measure of health risk. When gathered for the U.S. population, biomonitoring data can help to identify new chemicals that are found in the environment and in human tissues, monitor changes in exposures, and establish the distribution of exposures among the general population. The data can also be used to identify populations, such as infants and children, that might have higher exposures than the general population. State and local officials can use biomonitoring data to help to assess environmental risks in specific sites or populations (GAO 2000). In occupational and clinical medicine, biomonitoring can be used as a surveillance tool to help to interpret a clinical problem or to monitor an exposure trend.

Several salient examples highlight the contribution of biomonitoring data to robust public-health decisions and regulations. A case example is the measurement of blood lead, which has been extensively studied. Advances in biomonitoring have allowed scientists to measure blood lead at low concentrations and to correlate these concentrations with adverse health effects. That has resulted in the lowering by the Centers for Disease Control and Prevention (CDC) of blood lead concentrations of concern to 10 μg/dL, although no threshold for effects has been identified (CDC 2005). Blood lead concentrations collected in the CDC National Health and Nutrition Examination Survey (NHANES) from 1976 to 1980 provided impetus for Environmental Protection Agency (EPA) regulations that reduced lead in gasoline, in part on the basis of declining blood lead that paralleled declining gasoline lead (GAO 2000; Jackson et al. 2002).

[3]*Pharmacokinetics* is defined as "the quantitative study of factors that control the time course for absorption, distribution, metabolism, and excretion of chemicals within the body" (Reddy et al. 2005). Pharmacokinetics was developed based on studies with therapeutic drugs. Toxicokinetics is a more recent term that has essentially the same meaning as pharmacokinetics, but refers specifically to non-drug substances, primarily toxic chemicals (McNaught and Wilkinson 1997). The committee uses the term pharmacokinetics, and by analogy pharmacodynamics (biological effect of chemical interaction with target sites in the body), as these terms were originally used and many of the key principles were first described within the context of therapeutic drugs.

CURRENT BIOMONITORING ACTIVITIES

The widespread use of biomonitoring, as evidenced by reports citing chemical concentrations in human blood samples (CBRC 2005; IC Wales 2005; WWF 2002, 2003) or in initiatives for developing biomonitoring programs in such states as California and Minnesota (OMB Watch 2005; Risk Policy Report 2005), stems from improvement in analytic methods and laboratory techniques. It is possible to measure smaller concentrations of chemicals in the body and to do so with smaller quantities of biologic samples (such as blood and urine).

In 2001, 2003, and 2005, CDC published the *First, Second,* and *Third Reports on Human Exposure to Environmental Chemicals*. Those landmark publications reported the concentrations of chemicals and metabolites in blood and urine of a representative sample of the U.S. civilian population from NHANES, with the first report detailing 27 chemicals and the second and third 116 and 148 chemicals, respectively.

Other federal agencies have participated in biomonitoring efforts, including EPA, which sponsored the National Human Exposure Assessment Survey (NHEXAS) in the 1990s. NHEXAS stemmed from a recommendation in the 1991 National Research Council report *Monitoring Human Tissues for Toxic Substances* (NRC 1991) that the United States adopt a new program to monitor chemical residues in human tissues. NHEXAS, although not solely focused on biomonitoring, studied the exposure of hundreds of people in three areas of the United States to metals, pesticides, volatile organic compounds, and other chemicals. The survey was designed to evaluate the distribution of human exposure to multiple chemicals by multiple routes and from multiple sources and their association with environmental concentrations and personal activities. In addition, the National Children's Study—sponsored by the National Institutes of Health, CDC, and EPA—is a national longitudinal study that, if funded, would have the potential to examine environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth to the age of 21 years. The study would analyze a variety of environmental exposures, biomonitoring measures, and health effects (Needham et al. 2005).

CHALLENGES

Despite the powerful nature of biomonitoring (Wilhelm et al. 2004), the utility and interpretation of the data are controversial. The controversy stems in part from the fact that the pace at which biomonitoring data are being generated has eclipsed the development of basic epidemiology, toxicology, and exposure-assessment techniques that are needed to evaluate

whether a chemical measured in an individual or a population may cause a health risk and to determine its sources. Our technical ability to generate new biomonitoring data has essentially exceeded our ability to interpret them. Thus, it has become easier to measure chemicals or their metabolites in the body than to interpret or communicate the findings. As CDC states in its national-exposure reports, the findings of a chemical in people's blood or urine does not necessarily mean that it causes a health risk or disease (CDC 2005). The challenge for public-health officials is to understand the health implications of the biomonitoring data and to craft appropriate public-health policy responses.

Biomonitoring data are more challenging to interpret than other exposure measures, such as personal air sampling or exposure diaries, in that they provide information on internal doses that are integrated across environmental pathways and routes of exposure and directly reflect the amount of chemicals that are absorbed into the blood and are distributed, stored, metabolized, and excreted. Therefore, not only must the complexities of the biologic system be considered, but also the properties of the chemicals or their metabolites.

Because biomonitoring studies typically measure a concentration of a chemical in a biologic medium (such as blood or urine) without knowledge of when exposure to it occurred, the properties of the chemical or its metabolite that affect how long it remains in the body are critical in trying to understand the biomonitoring results. For persistent chemicals (chemicals that remain in the body for months or years, such as lead in bone or lipophilic organic chemicals in adipose tissue), biomonitoring data provide information on what chemical and how much enters the body and accumulates; in most cases, biomonitoring data do not provide information on the timing, sources, or routes of exposure. For chemicals that remain in the body for shorter periods, biomonitoring data may be much more difficult to interpret; timing and duration of exposure become more critical to the interpretation (Needham et al. 2005).

The most important question for biomonitoring efforts to address is whether exposure to a chemical causes health effects. Few data are available on most of the chemicals measured in population studies, such as NHANES, to address that question (Metcalf and Orloff 2004). For example, the Government Accountability Office (GAO 2005) reports that EPA has limited data on the health and environmental risks posed by chemicals now used in commerce. A survey of risk-assessment practitioners on the extent to which biomarkers are used in risk assessment concluded that the absence of chemical-specific data (for example, toxicologic and epidemiologic data) was the primary limitation in using exposure biomarkers in risk assessment (Maier et al. 2004).

At a minimum, one would like to determine the exposure distribution in a population to establish a "reference range."[4] A reference range can be used to compare individual or subgroup results. With additional analyses, one can determine whether some members of the population have higher exposures than others. However, a biomonitoring value above the upper bound of the reference range does not necessarily mean that there is a health risk, just as a value below the lower bound of the reference range does not mean that there is no health risk.

Putting biomonitoring information into a health-based context is important. It can be done by comparing biomonitoring values with health-based values on the basis of a combination of physiologically based pharmacokinetic modeling and toxicologic and epidemiologic data (described in Chapter 5). As indicated above, very few health-based values have been established for biomonitored chemicals, and there are inherent uncertainties in estimating health risks (discussed further in Chapter 5).

As discussed in Chapter 6, communicating health-based values and other conclusions based on biomonitoring data requires a full discussion of the inherent strengths and limitations of the original data and the related risk conclusions.

Table 1-1 shows that of the 148 chemicals measured by CDC in its third exposure report (CDC 2005), only 25 have established EPA reference values—reference concentrations (RfCs) or reference doses (RfDs)—and/or cancer potency factors. With respect to the occupational arena, only a few have Threshold Limit Value–time weighted averages (TLV-TWAs) and biologic exposure indices (BEIs). Because of the challenges of putting results of biomonitoring studies into context and because human subjects are involved, it is critical to factor communication and ethical considerations into the design, identification, and recruitment of subjects, the handling and use of data, and interpretation of results, including any risk-analysis and risk-management decisions that stem from biomonitoring efforts. The personal nature of biomonitoring raises the bar on ethical and communication challenges because the mere fact that biomonitoring data are results of measurements in human specimens gives them the appearance of being more accurate than traditional sources of exposure information, such as questionnaires and environmental monitoring (Schulte and Sweeney 1995). The challenges include addressing the biomonitoring results on an individual vs group level, the variability within and among individuals, the issue of multiple chemical exposures, and the varied exposures among a population.

[4]Reference ranges are biologic measurements obtained in a reference population, typically a population with no known exposure or only minimal exposure to the toxicant of concern (Pirkle et al. 1995).

TABLE 1-1 Numbers of Chemicals in *Third National Report on Human Exposures to Environmental Chemicals* for Which Health-Based Values Are Available

148[a]	Number of chemicals sampled by CDC in third national report
25	Number of chemicals for which EPA reference values (i.e., RfCs or RfDs) and/or cancer slope factors are established[b]
23	Number of chemicals for which TLV-TWAs are established
5	Number of chemicals for which BEIs are established
3	Number of chemicals for which RfDs/RfCs, TLVs, and BEIs are established

[a]The CDC measures 148 total analytes; however many are similar compounds that are members of a broader class of chemicals, such as polychlorinated biphenyls, dioxins and furans, organophosphorus pesticides, and heavy metals.

[b]Many of the chemicals do not have specific health-based values, but because many are in similar classes of compounds, alternative approaches to evaluate toxicity, such as toxic equivalency factors, are available.

Source: CDC 2005.

RfC (reference concentration) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

RfD (reference dose) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Cancer slope factors are upper bounds, approximating a 95% confidence limit, on the increased cancer risk posed by a lifetime exposure to a carcinogen (EPA 2006).

TLV-TWA is the Threshold Limit Value–time weighted average concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect (ACGIH 2001). In general, TLV-TWA values are used to derive BEIs (Biological Exposure Indices).

BEIs are the concentrations of chemicals that are most likely to be observed in specimens (blood or urine) collected from healthy workers who have been exposed to chemicals to the same extent as workers with inhalation exposure at the TLV. The exceptions are the BEIs for chemicals for which the TLVs are based on protection against nonsystemic effects (such as irritation or respiratory impairment) where biomonitoring is desirable because of the potential for substantial absorption via an additional route of entry (usually the skin). The BEI generally indicates a concentration below which nearly all workers should not experience adverse health effects (ACGIH 2001).

As Schulte and Sweeney (1995) state, "scientists like to think of gathering and interpreting data as being independent from the social and political context. . . ." But where controversies surround the issue of health risks, as they do in the case of biomonitoring data, the communication and ethical aspects cannot be divorced from the use of the data.

The key challenges in interpreting and using biomonitoring data are summarized in Table 1-2.

TABLE 1-2 Challenges to Interpreting and Using Biomonitoring Data

Challenge	Comment
Data requirements	Requires knowing properties of chemical or metabolite and complexities of biologic system
Lack of toxicologic, epidemiologic, and toxicokinetic data	Few data available to assist in determining whether presence of some concentration of a chemical in body may have health effect
Lack of health-based values for comparison	Few health-based values (such as RfDs, RfCs, cancer slope factors, or BEIs) are available to put biomonitoring results into context
Interpreting data for exposure assessment	Lack of data on sources of chemicals and how exposures occur makes efforts to identify and control exposures difficult
Interpreting data for health risk	Because of lack of data and absence of health-based values, it is possible to estimate health risks posed by only a very small fraction of chemicals that can be biomonitored
Communication and ethical challenges	Personal and complex biomonitoring data require careful planning, informed consent, information sharing, and evaluation to continue to move science of biomonitoring forward
Evaluating and informing the policy process	Once results from biomonitoring studies are understood, how can data be best used to evaluate and inform public-health decisions?

BIOMARKERS AND BIOMONITORING

Biologic indicators or biomarkers generally include biochemical, molecular, genetic, immunologic, or physiologic signals of events in biologic systems. The events are depicted as a continuum between an external exposure to a chemical and resulting clinical effect (Schulte and Perera 1993). Biomarkers have traditionally been classified as markers of exposure, effect, or susceptibility (see Figure 1-1).

With respect to environmental chemicals, biomarkers of exposure, effect, and susceptibility are defined as follows (WHO 2001):

Biomarker of exposure. The chemical or its metabolite or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism.

Biomarker of effect. A measurable biochemical, physiologic, behavioral, or other alteration in an organism that, depending on the magnitude,

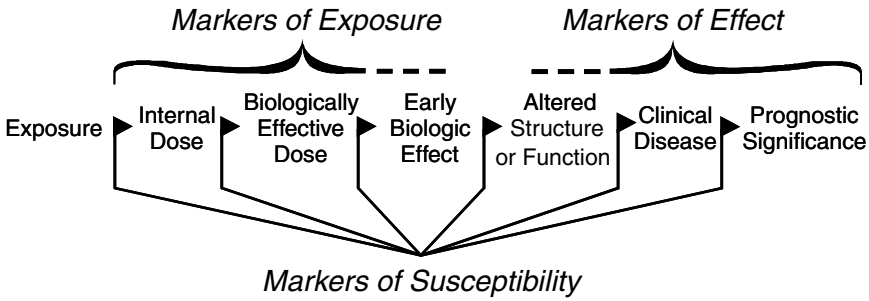

FIGURE 1-1 Simplified flow chart of classes of biomarkers. Source: NRC 1987.

can be recognized as associated with an established or possible health impairment or disease.

Biomarker of susceptibility. An indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific chemical substance.

Biomonitoring in the context of this report focuses on biomarkers of exposure, that is, the early stages in the process: internal dose (ID), biologically effective dose (BED), and early biologic effect (EBE). ID is the amount of a chemical or its metabolite found in a biologic medium (NRC 1987). BED is the amount of a chemical or its metabolite that interacts with critical subcellular, cellular, and tissue targets. BED represents the integration of external exposure, pharmacokinetics, and interaction of an active chemical form with a target site, such as DNA or a key enzyme. EBE represents an event correlated with, and possibly predictive of, a health effect (for example, lymphocyte chromosomal aberrations, as this effect occurs in a cell type that can be readily screened for the response occurring in the target tissue) (NRC 1987; Schulte and Perera 1993).

Because biomarkers lie on a continuum, it may be difficult to delineate between biomarkers of exposure and effect (Morgan 1997). However, in considering biomarkers in relation to the information that they provide, it is critical to think about what is known about them in terms of exposure vs health effect. (This is discussed in further detail in Chapter 3.) In addition, as scientific knowledge increases, our understanding of where biomarkers lie on the continuum may change (NRC 1987).

This report focuses primarily on biomonitoring as used in population-based studies, such as CDC's national reports on human exposure or EPA's NHEXAS, because they raise the most far-reaching and challenging questions regarding the interpretation of biomonitoring data. The population-

based studies sample a large number of chemicals; however, few data are available on most of them to determine the health risks posed by an elevated or even background concentration in a blood or urine sample. Because biomarkers of ID raise the greatest interpretive challenges in the large population-based studies, they are the focus of this report; biomarkers of EBE and BED are equally important, but they are not addressed in detail here.

The committee acknowledges that there has been substantial research developing biomarkers further along the exposure-effect continuum, including prominent work by Gan et al. (2004); Hecht (2003); Joseph et al. (2005); Kensler et al. (2005); Qian et al. (1994); Rappaport et al. (2005); and Yu et al. (1995). The ultimate objective of the biomonitoring research is to link biomarkers of exposure to biomarkers of effect and susceptibility to understand the public-health implications of exposure to environmental chemicals.

Some consideration will also be given to other applications of biomonitoring, beyond population-based studies, because it is being used for myriad purposes, and such uses cannot be ignored. Those applications include the broad categories of risk assessment and management—scoping, evaluating status and trends, conducting exposure and health research, and risk assessment—and are expanded on in Chapter 3.

THE NATIONAL RESEARCH COUNCIL COMMITTEE

To address some of the challenges raised by biomonitoring data, Congress[5] asked the National Academies to perform an independent study to identify key uncertainties in estimating exposure, health effects, and human risks potentially associated with biomonitoring and to develop a research agenda for interpreting human biomonitoring data.

In response, the National Research Council established the Committee on Human Biomonitoring for Environmental Toxicants, which prepared this report. Committee members were selected for their expertise in biomonitoring, analytic chemistry, public and environmental health, biostatistics, epidemiology, toxicology, dose-response modeling, toxicokinetics, exposure assessment, human health risk assessment, risk communication, and regulatory decision-making. Members come from universities and other organizations and serve pro bono. Committee members were asked to serve as individual experts, not as representatives of any organization.

The committee was charged with reviewing current practices and recommending ways to improve the interpretation and uses of human bio-

[5]In the conference report to accompany H.R. 2861, the Department of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriations Act, 2004.

monitoring data on environmental chemicals. The report identifies key principles and uncertainties in estimating and interpreting chemical exposures and health risks from biomonitoring data. The committee was also tasked with developing an overall research agenda for addressing uncertainties to improve evaluations and characterizations of health risks and to improve tracking of changes potentially relevant to public health.

To address its task, the committee held four public sessions in which it heard presentations from officials of EPA's Office of Research and Development; CDC's National Center for Environmental Health, National Center for Health Statistics, and National Institute for Occupational Safety and Health; the Washington State Department of Health; the International Life Sciences biomonitoring committee; the American Chemistry Council; CropLife America; the Association of Public Health Laboratories; Environmental Defense; and academe.

In addressing its charge, the committee was mindful of several facts. The impetus for the study was the abundance of biomonitoring data that indicated that large numbers of the population have very low concentrations of chemicals in their bodies and that the data and methods needed to interpret these concentrations were not available. Addressing the questions posed by biomonitoring results will require the interdisciplinary collaboration of scientists, public-health officials, and experts in communication and ethics. Therefore, this report is aimed at a diverse audience, including the public-health and medical communities, policy-makers, the federal agencies that sponsor biomonitoring research, and the public.

ORGANIZATION OF THE REPORT

The body of this report is organized into six chapters. Chapter 2 presents an overview of biomonitoring efforts in the United States and internationally. Chapter 3 lays out a systematic framework to characterize the properties of biomarkers and their significance when they are used in biomonitoring studies. Chapter 4 discusses considerations necessary in the design of biomonitoring studies, including communications and ethics. Chapter 5 lays out approaches to interpreting biomonitoring data that depend on the information available. Chapter 6 highlights the challenges that public-health officials face in communicating the results of biomonitoring efforts. Chapter 7 presents a research agenda for improving the interpretation and utility of biomonitoring data.

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2

U.S. and International Biomonitoring Efforts

Human monitoring of occupational exposures was conducted beginning in the 1890s through a variety of blood lead monitoring programs (Sexton et al. 2004). Population-based biomonitoring is more recent and has been implemented at various levels within the United States (both federally and among states) and internationally. Only with the recent advent of the National Health and Nutrition Examination Survey (NHANES) have population-based biomonitoring[1] studies expanded on measurements of lead, cadmium, and cotinine in clinical specimens (Burke and Sexton 1995). With the additional exposure surveillance data provided by NHANES and a variety of international biomonitoring efforts, regulators now have an improved understanding of how widespread some chemical exposures are in the general population. Biomonitoring data will improve our understanding of population and individual exposures to chemicals and will help regulatory agencies to set priorities for toxicologic and environmental-health research. Litt et al. (2004) noted that "new technologies in biomonitoring have the potential to transform the nation's capacity to track exposure to pollutants and understand their impacts on health."

Current biomonitoring efforts can be categorized as survey projects and research projects. The objective of survey projects typically is to advance public health by producing information about the prevalence of exposure to environmental toxicants based on periodic monitoring (European

[1]As stated in Chapter 1, biomonitoring in the context of this report is focused on biomarkers of exposure, that is, it is limited to the early stages in the process: internal dose, biologically effective dose, and early biologic effect.

Commission 2004; Knudsen 2004, as cited in ECETOC 2005). Research projects typically are hypothesis-driven and geared to the collection of data to link health outcomes causally to exposures (ECETOC 2005).

Selected historical and current U.S. and international large-scale, population-based efforts to monitor environmental toxicants in human tissues are summarized below. Also included is a brief discussion of biomonitoring by private organizations and laboratories. This chapter is meant not to be a comprehensive summary of biomonitoring efforts but to provide context on the history of biomonitoring and on current and planned efforts in the field. This overview illustrates the diversity in current biomonitoring efforts, particularly with respect to study population size and analytes measured. Because of the differences in biomonitoring studies, including the type of studies conducted, when the studies were performed, and the various applications for the biomarkers, the committee explicitly did not address the duration of the biomonitoring studies or their respective costs in this chapter.

HUMAN BIOMONITORING IN THE UNITED STATES

Population-based biomonitoring programs in the United States have been in place since the late 1960s and have evolved substantially (see Figure 2-1). Such initial efforts as the National Human Monitoring Program, administered by the U.S. Environmental Protection Agency (EPA), and NHANES, administered by the Centers for Disease Control and Prevention (CDC), monitored for only a few chemicals, primarily pesticides and metals. Later efforts, including the National Human Exposure Assessment Survey (NHEXAS) and NHANES (1999-2000), began monitoring for many more chemicals. In addition to monitoring for a greater variety of chemicals, some studies (NHEXAS and the Agricultural Health Study) began to include environmental sampling to quantify personal exposure better. Although the larger population-based efforts (such as NHANES) have not been able to incorporate environmental monitoring, they have been instrumental in collecting background information on exposure to upwards of 140 chemicals. In the future, the National Children's Study (NCS), if funded, would have the potential to collect biomonitoring data and link them to environmental monitoring data.

CDC has been a major player in funding both state and national biomonitoring programs. NHANES and the *National Reports on Human Exposure to Environmental Chemicals* have provided regulators with a comprehensive overview of exposures in the general population to selected chemicals.

Improvements in analytic techniques for sampling, including lower detection limits, will probably change how biomonitoring data are used. It

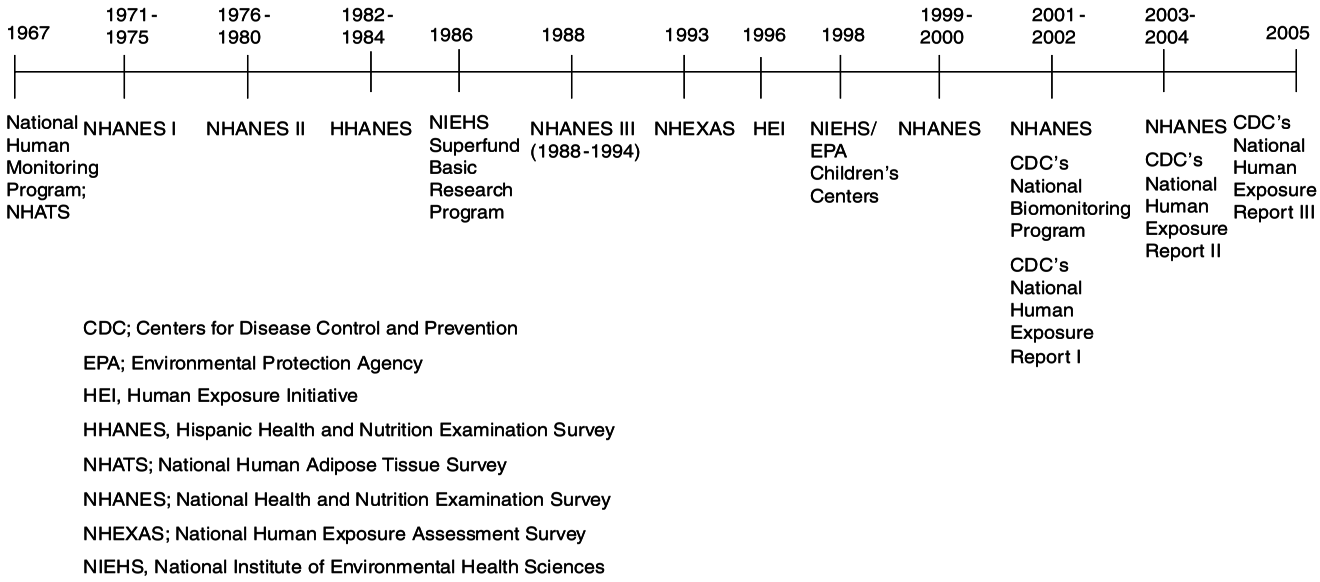

FIGURE 2-1 Timeline of major U.S. biomonitoring efforts.

also appears that there may be more focus on state and local monitoring through federal funding (the CDC National Biomonitoring Program, NBP) and legislated efforts (as in California and Minnesota). And the monitoring of chemicals in children could be a priority if the NCS is funded.

A majority of U.S. biomonitoring efforts measure such analytes as heavy metals, pesticides, cotinine, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins, phthalates, and volatile organic compounds (VOCs). Future population-based studies (such as NHANES) will include such chemicals as perfluorinated compounds, polybrominated diphenyl ethers (PBDEs), and perchlorate, on which little exposure information is available.

The National Human Monitoring Program and the National Human Adipose Tissue Survey

EPA has been involved in a number of biomonitoring efforts, including the National Human Adipose Tissue Survey (NHATS). One of the earliest biomonitoring efforts was the National Human Monitoring Program (NHMP). NHMP was established in 1967 by the U.S. Public Health Service to study pesticide exposures in the population. A primary component of NHMP was the NHATS. NHATS, inherited by EPA in 1970, measured pesticides in human adipose tissue to identify chemicals to which a representative sample of the U.S. population was being exposed and to set priorities for reducing risk posed to at-risk groups (NRC 1991). Since its inception, NHATS has collected nearly 12,000 samples of human tissue, primarily from cadavers and some from patients, and provided adequate data to document the extent of exposure of the U.S. population to over 130 pesticides (NRC 1991).

In 1990, the National Research Council Committee on National Monitoring of Human Tissues reviewed and evaluated the uses and effectiveness of NHMP (NRC 1991). In its review, the committee noted that NHATS was effective in documenting a "widespread and significant prevalence of pesticide residues in the general population" and showed "that reductions in use of PCBs, DDT, and dieldrin have been followed by a decline in measured concentrations of these compounds" (NRC 1991). The committee's review of the program, with its discussion of the need for improved monitoring, was the impetus for the development of NHEXAS.

The National Human Exposure Assessment Survey

NHEXAS was established in 1993, as a follow on to NHATS, to evaluate comprehensive human exposure to multiple chemicals on a community and regional scale (EPA 2005). NHEXAS expanded on NHATS by moni-

toring chemicals (including lead, other metals, pesticides, and organic chemicals) in blood and urine and by surveying personal exposures to chemicals through environmental sampling of air, water, and soil and dust and personal monitoring of air, food and beverages, and uptake (EPA 2005; NRC 1991). Three pilot surveys were conducted: in Arizona, in Maryland, and in a sample population of people in Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin (EPA 2005). NHEXAS measured 46 chemicals in about 460 people (NRC 1991). An EPA Science Advisory Board (SAB) report reviewing NHEXAS noted that among the major strengths of its design were that it was possible to "track many of the exposure pathways back to sources of exposure and [that it] provides a sound scientific basis for exposure and risk reduction" (EPA SAB 1999). The SAB report also recommended that NHEXAS be linked with NHANES data.

Other current federal efforts that incorporate biomonitoring include the National Institute of Environmental Health Sciences (NIEHS)-U.S. EPA Centers for Children's Environmental Health and Disease Prevention Research, the NIEHS Superfund Basic Research Program, and CDC's NHANES and the *Reports on Human Exposure to Environmental Chemicals*. NHANES remains the largest and most comprehensive effort to study chemicals in the U.S. population. If funded, future national biomonitoring efforts would include the NCS, a longitudinal study of children from when they are in utero to the age of 21 years that would incorporate regular biomonitoring for environmental chemicals. CDC's NHANES and the *Reports on Human Exposure to Environmental Chemicals,* the NIEHS-EPA Centers for Children's Environmental Health and Disease Prevention Research, and the NCS are highlighted below. Details on other federal programs, including NIEHS's Superfund Basic Research Program, are presented in Table 2-1.

National Institute of Environmental Health Sciences-Environmental Protection Agency Centers for Children's Environmental Health and Disease Prevention Research

The NIEHS-EPA Centers for Children's Environmental Health and Disease Prevention Research conduct an array of observational studies of environmental-related diseases in children. The program, initiated in 1998, was designed to study environmental exposures of infants and young children, link the exposures to health effects, and develop intervention strategies for reducing the exposures. Funded in two phases, the program includes 12 centers (Kimmel et al. 2005; Landrigan and Tamburlini 2005). Each center has a unique and varied research focus and includes studies of respiratory diseases, childhood learning issues, and developmental disabilities, among others (Kimmel et al. 2005).

TABLE 2-1 Examples of Current U.S. and International Biomonitoring Efforts

Agency/Organization/State	Biomonitoring Program
United States	
National Institute of Environmental Health Sciences-Environmental Protection Agency Centers for Children's Environmental Health and Disease Prevention Research	Twelve centers established to conduct observational studies of environmental exposures of children. Centers are collecting a variety of human tissue and samples, including urine, breast milk, peripheral blood, cord blood, meconium, vernix, saliva, hair, placental tissue (Eskenazi et al. 2005).
Centers for Disease Control and Prevention—National Health and Nutrition Examination Surveys (NHANES); *National Reports on Human Exposure to Environmental Chemicals*	Provides continuing assessment of U.S. population's exposure to environmental chemicals using biomonitoring data from NHANES. First *National Report on Human Exposure to Environmental Chemicals* (First Report) was issued in March 2001. Second Report, released in January 2003, presents biomonitoring exposure data on 116 environmental chemicals for noninstitutionalized, civilian U.S. population in 1999-2000. Third report was released in July 2005 and includes data on 148 chemicals (CDC 2005).
Centers for Disease Control and Prevention—State funding through National Biomonitoring Program (see discussion of state biomonitoring efforts below)	In 2001, CDC's Environmental Health Laboratory launched planning grant program (National Biomonitoring Program) to support biomonitoring capacity building for state public-health laboratories (CDC 2005).
Agency for Toxic Substances and Disease Registry (ATSDR)	ATSDR conducts site-specific exposure investigations, many of which use biomonitoring to assess individual exposures. For example, ATSDR's Great Lakes Human Health Effects Research Program works to characterize exposure to persistent contaminants via consumption of Great Lakes fish, to investigate potential adverse health effects, and to identify vulnerable subpopulations. Exemplary biomonitoring-based investigations include effects of Great Lakes fish consumption on body burdens of dioxins, furans, and PCBs (Anderson et al. 1998; Falk et al. 1999) on motor functioning in ageing fish-eaters (Schantz et al. 1999), on reproduction-related endpoints (Persky et al. 2001; Karmaus et al. 2002; Buck et al. 2003), and on behavior and memory (Schantz et al. 2001; Stewart et al. 2003). Vulnerable populations studied under this program include Native Americans (Dellinger et al. 1996; Fitzgerald et al. 1999), neonates (Lonky et al. 1996; Stewart et al. 2000), and the aged (Schantz et al. 1999, 2001).

Chemicals Measured
Mercury, lead, cotinine, pesticides, phthalates, PAHs, PAH-DNA adducts, allergens, endotoxin, antioxidant micronutrients, cytokines, immunoglobulin E, cholinesterase, thyroid hormones, DNA polymorphisms
Lead, cadmium, mercury, cobalt, uranium, antimony, barium, beryllium, cesium, molybdenum, platinum, thallium, tungsten, organochlorine pesticides, organophosphorus insecticides (dialkyl phosphate metabolites), (specific metabolites), pyrethroid pesticides, other pesticides (2-isopropoyxyphenol, carbofuranphenol), herbicides, phthalates, phytoestrogens, polycyclic aromatic hydrocarbons, polychlorinated dibenzo-*p*-dioxins and dibenzofurans, polychlorinated biphenyls, tobacco smoke

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
National Institute of Environmental Health Sciences Superfund Basic Research Program	Funds peer-reviewed research in 19 university programs encompassing 70 collaborating institutions (including number of biomonitoring programs) (NIEHS 2005). For example, the Universities of North Carolina, Chapel Hill (UNC) and California, Berkeley (UCB) are conducting studies to develop and validate biomarkers of exposure to benzene and arsenic with which to investigate exposure response relationships in humans.
Agricultural Health Study	Large prospective cohort study, conducted in North Carolina and Iowa, to assess current and past agricultural exposures using interviews and environmental and biologic monitoring. Evaluating relationship between pesticide exposure and the development of specific cancers (Alavanja et al. 1996; Agricultural Health Study 2005).
Farm Family Exposure Study (FFES)	FFES was designed to study pesticide exposures of farm families by measuring urinary pesticides in applier, spouse, children (Farm Family Exposure Study 2005).
California	California Department of Health Services Environmental Health Laboratory Branch developed California Biomonitoring Plan under 2-year grant from CDC (APHL 2004).
Iowa, Minnesota, North Dakota, South Dakota, and Wisconsin	Biomonitoring consortium of five Upper Midwest states. States plan to share biomonitoring data and samples on toxicants (CDC 2005).
New Hampshire	Developing public-health laboratory capacity to biomonitor for arsenic, mercury, phthalates, polybrominated diphenyl ethers; and planning pilot studies to estimate body burden of environmental toxicants using newly developed biomonitoring analytic methods (CDC 2005).
New York	Developing capacity to monitor for polyaromatic hydrocarbons (PAHs) in urine, polybrominated diphenyl ethers (PBDEs) in serum, organochlorine pesticides in serum, volatile organic compounds (VOCs) in blood, cotinine in saliva, trace elements in blood and urine, inorganic mercury in blood; and to generate data on exposure to persistent organic pollutants (CDC 2005).

Chemicals Measured
Pesticides
Pesticides (glyphosate, 2,4-D, 3,5,6-trichloro-2-pyridinol (chlorpyrifos))
Organochlorines (DDT), organophophorus dialkyl phosphate metabolites, pyrethroids, PCBs, PBDEs, phthalates, lead, mercury
Asbestos, nitrates and nitrites, persistent organic pollutants, selenium
Arsenic, mercury, phthalates, polybrominated diphenyl ethers
PAHs, PBDEs, organochlorine pesticides, VOCs, cotinine, trace elements, inorganic mercury

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
Pennsylvania	Currently funding biomonitoring and environmental-health tracking efforts, including studies of people living in the vicinity of coal-burning power plants.
Washington	Efforts to enhance environmental monitoring and analyses of mercury and polychlorinated biphenyls, as well as other persistent toxicants.
Rocky Mountain Biomonitoring Consortium (RMBC)	RMBC includes Arizona, Colorado, Montana, New Mexico, Utah, and Wyoming in efforts to implement and expand regional laboratory-based biomonitoring program. Program will assess extent of exposure to environmental toxicants, including collecting data on background exposures (CDC 2005).
American Chemistry Council Long-Range Research Initiative (LRI)	LRI has signed a memorandum of understanding with EPA for joint grant solicitations to fund projects to identify methods and approaches for future population studies requiring exposure information, for studies that characterize exposure factors that are related to high-end exposures, and to interpret biomonitoring data in relation to the exposure data. Some current projects are: "(1) comparing biomonitoring data to exposure data in an attempt to better interpret ethylene oxide DNA adducts (i.e., ethylene oxide bound to DNA) and urine and blood levels of benzene metabolites, respectively, (2) studying the relationship between exposure to phthalates and urinary biomarkers in rats and then modeling this relationship for humans, (3) developing and applying more advanced statistical models to characterize relationships between exposures and biomonitoring data, and (4) evaluating biomarkers of in utero exposures to background levels of environmental contaminants" (LRI 2005).
Canada	
Canadian Health Measures Survey	Beginning in 2006, Statistics Canada will initiate a national survey of 5,000 people to collect data on health status and biological measurements to assess exposures to environmental chemicals, including lead and mercury. The surveys are currently in development and collection of data is expected to begin in the fall of 2006, with results released in 2009 (Statistics Canada 2006).

Chemicals Measured
Heavy metals (lead, arsenic, mercury)
Arsenic, cotinine, DDT, dioxins, lead, PBDEs, PCBs, mercury, cholinesterase, trihalomethanes
Heavy metals, arsenic speciation, mercury speciation, organophosphates, organochlorine pesticides, VOCs, dichloroethane, trichloroethylene; cotinine, nitrates and nitrites, creosote, PAHs (wood smoke), radionuclides, cyanide, dioxin-furan, disinfection byproducts, perchlorates, phthalate metabolites, thiodiglycol (mustard gas), sarin

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
European Union	
Science, Children, Awareness-Raising, Legal Instruments and Evaluation (SCALE)	SCALE program is designed in effort to "develop a coherent approach to biomonitoring in Europe." SCALE Working Group aims to "(1) examine the range of policy relevant objectives for human biomonitoring and identify those which are suitable for an EU approach; (2) develop comparable protocols addressing initiation, performance and followup of biomonitoring activities; (3) develop scenarios to integrate biomonitoring results with environmental monitoring data and health monitoring data; and (4) develop communication strategies to allow for adequate responses." (European Commission 2004)[a]
Belgium	
Center for Environmental Health: Flemish biomonitoring program for surveillance of environmental health	Program will include development of an early warning system based on biomarker measurements in people living in Flanders. Study population includes 1,600 people (European Commission 2004).
FONIA study—follow-up study of newborns regarding immunologic development and its relation to atopy	Assessing immunologic development and its relation to allergies in children (European Commission 2004).
Croatia	
Exposure, Intake, and Effects of Toxic and Essential Elements	Assessment of steroid hormone disruption in placenta as indicator tissue for monitoring fetal and maternal environment. Biomonitoring of metals is included with evaluation of dietary metal intake (European Commission 2004).
Institute for Medical Research and Occupational Health, Zagreb: persistent organic pollutants (POPs) in human milk	Study will monitor concentration and distribution of POPs in human milk and daily intakes by children who are breast-fed (European Commission 2004).

[a]A number of the EU efforts discussed in this table were identified from an inventory of biomonitoring efforts in European Commission (2004) report. This inventory is currently in the process of being continuously updated.

Chemicals Measured
Cadmium, lead, PCBs, dioxins, chlorinated pesticides
In vitro cytokine secretion in relation to allergen exposure
Lead, cadmium, mercury, arsenic, iron, zinc, copper, selenium, steroid hormone
Organochlorine pesticides, PCBs, PCDDs-PCDFs

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
Denmark	
ChildrenGenoNetwork	Study of gene-environment interactions during fetal, neonatal, and infancy periods, evaluating genotoxic exposures and environmental factors, including air pollutants (University of Copenhagen 2005).
Finland	
Biomonitoring of dioxins in breast milk	Measurements of dioxins in breast milk.
France	
EDEN	Study was initiated to identify factors associated with allergies and respiratory diseases in children, using biomarker data on heavy metals in cord blood, placenta, and hair and cotinine in cord blood and hair (European Commission 2004).
Endocrine disrupters: a longitudinal study on pregnancy and child (PELAGIE)	Study of exposure to environmental pollutants and pregnancy and postnatal development (European Commission 2004).
European Prospective Investigation into Cancer and Nutrition (EPIC)	Large study (over 500,000 participants) designed to investigate relationship between diet, nutritional status, lifestyle, and environmental factors and incidence of cancer and other chronic diseases. Blood samples are banked for future analyses (IARC 2005).
ISAAC-II	Study is evaluating health effects related to exposure to indoor pollutants in children (European Commission 2004).
Germany	
Cohort study on influence of persistent organic pollutants (POPs) exposure on neurodevelopment of children	Study will examine role of POP exposure on neurobehavioral development of children (European Commission 2004).

Chemicals Measured
Air pollutants, tobacco smoke, cytogenetic biomarkers
Dioxins, furans, PCBs, PBDEs, heavy metals
Heavy metals, cotinine
Glycol ethers, trichloroacetic acid, atrazine, PCBs, dioxin-like compounds
Primarily study of nutrition
Allergens, air pollutants, mold, and endotoxins
Lead, cadmium, PCDD/PCDF and PCBs

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
German Environmental Specimen Bank	Established to systematically collect, process, characterize, and store environmental samples. Blood and other human specimens have been collected since 1981 from about 100 unexposed persons (German Federal Environmental Agency 2006).
German Human Biomonitoring Commission	Commission draws up monographs on chemicals and derives reference and human biomonitoring (HBM) values. Commission has derived HBM values of lead, cadmium, mercury, and PCP. Commission is responsible for German Environmental Surveys which are representative population studies to determine the exposure of Germany's general population to chemicals. Surveys have been conducted in 1985-1986 (GerESI), 1990-1992 (GerESII), 1998 (GerESIII), 2003-2006 (GerESIV) (GerES 2005).
Influence of lifestyle factors and behavior on development of immune system and allergies in East-West settlement (LISA) Studying school beginners in Saxony-Anhalt	Study will assess role of indoor exposures on children and associated characterization of allergies (European Commission 2004). Study will investigate impact of environment on health of schoolchildren in industrial and nonindustrial areas of Saxony-Anhalt (European Commission 2004).
Luxembourg	
LNS/ALMEN/CST/AKUT: Impact of heavy metals and molds on environmentally burdened patients	Study will evaluate immunologic biomarkers and assess heavy metals in serum and/or hair samples (European Commission 2004).
Netherlands	
Association between chemical features of fine particulate air pollution and respiratory health of schoolchildren	Study was designed to investigate whether exposure to metals and particulate air pollution is associated with airway inflammation, reduced lung function in schoolchildren (European Commission 2004).
Generation R: The Rotterdam Study into Growth, Development and Health	Study will evaluate normal and abnormal growth and development and identify biologic, social, and environmental determinants (European Commission 2004).

Chemicals Measured
Aluminum, arsenic, barium, cadmium, calcium, copper, chromium, iron, lead, magnesium, manganese, mercury, nickel, phosphorus, potassium, selenium, sodium, sulfur, thallium, zinc, aldrin, dichlorodiphenyldichloroethane, dichlorodiphenyldichlorethene, dieldrin, hexachlorobenzene, heptachlorepoxide, hexachlorocyclohexane, dichlorodiphenyltrichloroethane (DDT), PCBs, pentachlorophenol, P,P′-DDT
Lead, cadmium, mercury, PCBs, DDE, HCB, HCH, arsenic, nickel, creatinine, cotinine, nicotine, cortisol, epinephrine, norepinephrine, pentachlorophenol and other chlorophenols, metabolites of pyrethroids, PAHs, organic esters of phosphoric acid
Reference ranges have been established for arsenic, lead, cadmium, mercury, platinum, nickel in blood and urine; pentachlorophenol and metabolites of organophosphorus in serum and urine; PCBs, ß-HCH, HCB, DDE in blood; organochlorine pesticides (ß-HCH, HCB, total DDT) in human milk
Metabolites of benzene, toluene, nicotine
Heavy metals (cadmium, mercury)
Heavy metals, molds
PM_{10}, $PM_{2.5}$, exhaled NO
Pesticides, phthalates, bisphenol A, cotinine

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
NEWGENERIS (Newborns and genotoxic exposure risks)	Using 300,000 mother-child birth cohorts and stored specimens from biobanks, study will develop and apply biomarkers of dietary exposure to genotoxic and immunotoxic chemicals and biomarkers of early effects (European Commission 2006). Researchers will analyze blood samples from biobanks in Norway, Denmark, the United Kingdom, Spain, and Greece (European Union 2006).
Norway	
Den norske Mor og barn undersøkelsen	Study will follow 100,000 pregnant women to assess potential exposures to mother and child as evaluated after delivery (European Commission 2004).
Poland	
DNA damage in children environmentally exposed to lead with assessment of individual susceptibility to toxic effect of lead, and genetic polymorphism of lead biotransformation and mechanism of DNA repair	Study will assess role of lead exposure in cytogenetic damage in children (European Commission 2004).
Environmental Cancer Risk, Nutrition, and Individual Susceptibility (ECNIS)	Studying use of biomarkers of exposure and susceptibility and bioindicators of disease in molecular epidemiology of cancer (ECNIS 2005).
Studies of Blood Lead	Systematic studies of blood lead in general population (Jakubowski 2004).
Portugal	
Environmental Health Survey Programs (ProVEpAs)	ProVEpAs are two regional environmental health survey programs carried out in Portugal: "1) to monitor prevalence, space and time trends of human exposure to emissions from Solid Waste Incinerators (SWI); 2) to analyze potential public health impact, either on relevant pathologies or health conditions." Biomonitoring will be conducted in several population groups (newborn-mother pairs, children under 6 years old, adults 18-65 years old in general population) (Reis et al. 2004).

Chemicals Measured
Dioxins, PCBs, ethanol, contaminated food, tobacco smoke, polluted air
Blood samples
Presence of mutagenic substances in urine, 1-hydroxypyrene, cotinine, cadmium in urine; lead in blood; selenium in serum; aromatic-DNA adducts
Lead
Heavy metals, dioxins, dioxin-like compounds

continued

TABLE 2-1 continued

Agency/Organization/State	Biomonitoring Program
Slovakia	
European Longitudinal Study of Pregnancy and Childhood (ELSPAC)	Study of role of biologic, environmental, and social factors in survival, health, development of fetus, infant, child (European Commission 2004).
Sweden	
Swedish Environmental Protection Agency: National Health Related Environmental Monitoring Program	Projects focused on exposure through air and food, including monitoring organic pollutants in breast milk and intake of pollutants in foods. Several studies include monitoring for metal and organic pollutant concentrations in human specimens. Human specimen bank is also storing human samples.
United Kingdom	
Avon Longitudinal Study of Parents and Children	Study includes 14,000 pregnant women and their children and includes collection of environmental, dietary, personal, and socioeconomic data and clinical data and biologic samples (European Commission 2004).
Placental Uptake and Transfer of Environmental Chemicals Relating to Allergy in Childhood Years (PLUTOCRACY) (Belgium, Slovakia, Romania)	Study has been designed to "link the kinetics of the placental transfer of xenobiotics with the epidemiologic associations of allergic diseases among children" (European Commission 2004).
Japan	
Ministry of Health, Labor, and Welfare	Continuing biomonitoring projects, including study of umbilical cord blood, maternal blood, milk.
New Zealand	
Ministry of Health	Ministry of Health is biomonitoring dioxin in population.
World Health Organization	
Breast-milk monitoring	WHO has conducted global surveys of dioxins, dibenzofurans, dioxin-like PCBs in human milk. Fourth UNEP/WHO protocol includes analysis of at least 50 individual samples of breast milk in each participating country (WHO 2005).

Chemicals Measured
Cadmium, lead, pesticides
Heavy metals (including mercury, cadmium), organic pollutants, allergic responses
Heavy metals, lead, cadmium, organochlorine insecticides, PCBs
Dioxins of PCDDs-PCDFs, PCBs
Dioxins
Dioxins, dibenzofurans, dioxin-like PCBs

Several centers have been collecting human samples, including urine, breast milk, peripheral blood, cord blood, meconium, vernix, saliva, hair, and placental tissue (Eskenazi et al. 2005). The samples have been analyzed for the presence of numerous substances, such as mercury, lead, cotinine, pesticides, phthalates, PAHs, PAH-DNA adducts, allergens, endotoxin, antioxidant micronutrients, cytokines, immunoglobulin E, cholinesterase, and thyroid hormones. The centers have also been storing samples for future research purposes (Eskenazi et al. 2005).

Centers for Disease Control and Prevention

Since the 1960s, NHANES has been monitoring nutritional and clinical factors in the U.S. population; chemicals in blood and urine were included recently. In addition, CDC's *National Reports on Human Exposure to Environmental Chemicals*, based on NHANES data, have been influential in setting priorities for future biomonitoring research (Schober 2005).

National Health and Nutrition Examination Survey

The National Health Survey Act of 1956 required the National Center for Health Statistics to begin collecting health statistics on the general U.S. population. The first health surveys were conducted from 1960 to 1962 on a small sample of the population 18-74 years old with additional surveys conducted on children, 6-17 years old (NRC 1991). Subsequent surveys, called the National Health and Nutrition Examination Surveys, included medical examinations and nutritional and dietary information on the study population.

Designed to study a probability sample of the noninstitutionalized civilian population of the United States, NHANES also conducted nutritional assessment of three high-risk populations: preschool children (6 months to 5 years old), those 60-74 years old, and the poor (persons below the poverty level) (NRC 1991). Each year, the current NHANES samples 5,000 persons, representative of the U.S. civilian household population, in 15 geographic locations. There is also an effort to oversample some demographic groups, including blacks and Mexican Americans (Schober 2005).

The first survey, NHANES I (1971-1975), did not monitor for any environmental chemicals. Later surveys, including NHANES II (1976-1980) and Hispanic HANES (1982-1984), collected data on chemicals by measuring lead and organochlorine pesticides (NCHS 1985). NHANES III measured lead, cadmium, selenium, and cotinine (Needham 2005). In the 1999-2000 NHANES, 116 chemicals were monitored; and the 2003-2004 survey monitored about 250 chemicals (Schober 2005; Needham 2005).

Needham et al. (2005a) discussed a number of limitations of NHANES, which include the following:

- Little blood, particularly from children, is available for biomonitoring analyses, because most of the collected samples are used for clinical and nutritional testing.
- NHANES collects only limited biomonitoring data on exposures of the fetus, infant, young and older toddler, and preschool-aged child.
- NHANES may capture some information on highly exposed populations, but it does not target them.

National Reports on Human Exposure to Environmental Chemicals

The first *National Report on Human Exposure to Environmental Chemicals* was initially released in 2001 and is based on analyses of NHANES biomonitoring data on exposure to chemicals. The data have various uses: to determine which chemicals people are exposed to and at what concentrations; to establish reference ranges for assessing whether an individual or group has an unusually high exposure, including susceptible populations, such as children, the elderly, and women of childbearing age; to track exposure trends; to assess the effectiveness of public-health efforts to reduce exposure of Americans to specific chemicals; and to set priorities for research on human health effects (CDC 2005).

The first report included an analysis of 27 chemicals for 1999; the second, released in 2002, included an analysis of 116 chemicals for 1999-2000, including the 27 from the first report (CDC 2003). The third report, released in July 2005, includes 148 chemicals for 2001-2002 (CDC 2005). The analytes measured in the third report are listed in Table 2-1. The third report includes newly established biomarkers (phthalates), lower limits of detection (of dioxins, furans, and PCBs), and reference ranges for chemicals not previously monitored (pyrethroid insecticides, phthalates, additional dioxins, PCBs, and other pesticides and herbicides).

The fourth report, to be released in 2007, will include nearly 300 analytes. A high-priority dataset of chemicals—including speciated forms of arsenic, perchlorate, PBDEs, and perfluorooctane sulfonate, and other perfluorinated compounds—may be released in 2006 to assist with regulatory decisions (James Pirkle, CDC, personal commun., June 21, 2005).

The criteria for including chemicals in the *National Reports on Human Exposure to Environmental Chemicals* include the following considerations: (1) whether exposure is changing (increasing or decreasing) or persisting; (2) health effects of exposure, (3) the proportion of the U.S. population exposed; (4) the need to assess the efficacy of public-health actions to reduce exposure; (5) existence of an analytic method for measuring the

chemical or its metabolite in blood or urine with adequate accuracy, precision, sensitivity, specificity, and speed; and (6) incremental costs (in dollars and personnel) to perform the analyses. CDC weights those criteria; items 1-3 receive the greatest weight, items 4 and 5 receive less weights (but the same weight as each other), and item 6 receives the least weight (67 Fed. Reg. 62477 [Oct. 7, 2002]).

CDC is developing formal criteria for delisting chemicals from the *National Reports on Human Exposure to Environmental Chemicals*, which it plans to publish in the Federal Register. Delisting criteria will consider whether there has been a change in the concentration of a chemical; if not, the chemical may be delisted (Pirkle 2005).

The biomonitoring data presented in each of the national exposure reports include descriptive statistics on the distribution of blood or urine concentrations of each chemical, including geometric means and percentiles with confidence intervals (CDC 2003). Each report also includes brief toxicity profiles and information relating the findings to biological exposure indices and European reference values or ranges, if available. Additionally, the raw data from the reports are publicly available and serve as a valuable resource.

The use of the *National Reports on Human Exposure to Environmental Chemicals* has a number of limitations, including the following:

- For most of the monitored chemicals, information for defining health-based reference values is not available.
- Environmental-exposure monitoring is not conducted in coordination with the biomonitoring.
- The number of ethnic groups and geographic locations sampled may limit the ability to extrapolate the data, in that exposure to chemicals may differ by ethnicity and geographic location (Schober 2005).
- Data on susceptible populations—including infants, toddlers, and preschoolers—are limited.
- The printed versions of the reports do not include data below the 50th percentile.
- There appear to be only limited strategies in place for communicating the reported results.
- The reports are based on a probability sampling of the U.S. population and cannot target "hot spots" of exposure.

Despite those limitations, the *National Reports on Human Exposure to Environmental Chemicals* are the most comprehensive available summaries of biomonitoring data on a representative sample of the U.S. population. The data provide reference ranges for numerous chemicals and will include, in future reports, data on chemicals which have recently become available,

such as PBDEs and perfluorinated compounds. Tests for trends in chemical exposures were not included in the most recent report (CDC 2005), because three survey periods are needed to establish these patterns; future reports will include such tests (NCHS 2005).

The National Children's Study

The President's Task Force on Environmental Health Risks and Safety Risks to Children was charged with "developing strategies to reduce or eliminate adverse effects on children (up to 21 years of age) caused by environmental exposures" (Needham et al. 2005b). The task force recommended that exposure be defined broadly to include biologic, chemical, physical, and psychosocial factors. The task force's assessment included a recommendation for a longitudinal cohort study of the effects of environmental exposure on the health of the nation's children. The Children's Health Act of 2000 authorized the National Institute of Child Health and Human Development to conduct this study with the assistance of CDC, NIEHS, and EPA (Needham et al. 2005b). However, the administration has targeted the NCS for elimination in its fiscal year 2007 budget request, and funding for the study is being debated.

The NCS is intended to follow a representative population of 100,000 children from conception to the age of 21 years and would analyze environmental exposures in the home and biomonitoring measures (CDC 2003). Previous studies of health effects related to environmental exposures of children have been limited by small samples, collection of data on only a few chemicals at a time, an inability to examine gene-environment interactions, and a lack of detailed exposure-assessment data (Trasande and Landrigan 2004). The NCS has the potential to be unique, in that it has been designed to study an extensive cohort of children—over a long period, to collect both biomonitoring data and exposure histories, and to consecutively monitor exposure to numerous chemicals (Trasande and Landrigan 2004). In addition, children are to be screened genetically, allowing for analysis of gene-environment interactions (Transande and Landrigan 2004).

Pesticide-Exposure Studies

Two studies of pesticide exposure in farm workers that include biomonitoring are the Agricultural Health Study (AHS) and the Farm Family Exposure Study (FFES). They include biomonitoring of organochlorine pesticides (AHS), glyphosate (FFES), 2, 4-D, and chlorpyrifos (FFES) in serum, urine, and buccal cells. The studies were designed to evaluate health risks related to pesticide exposure in potentially highly exposed populations.

Agricultural Health Study

The AHS, a collaborative research effort between the National Cancer Institute of the National Institutes of Health and EPA, is a prospective occupational study of 89,658 pesticide appliers and their spouses in Iowa and North Carolina "assembled between 1993 and 1997 to evaluate risk factors for disease in rural farm populations" (Blair et al. 2005). It is being conducted in three phases—phase I (1993-1997), phase II (1999-2003), and phase III (2005)—and includes only limited biomonitoring. Data are gathered with questionnaires to determine pesticide use and exposures, work practices, and other relevant exposures; from buccal cell collection; with dietary surveys; and with interviews to determine updated pesticide exposures (Agricultural Health Study 2005).

Farm Family Exposure Study

Conducted by the University of Minnesota, the FFES is a study of pesticide workers that includes limited biomonitoring. About 95 farm families in Minnesota and South Carolina are involved in regular monitoring of pesticide exposure (Farm Family Exposure Study 2005). After pesticide exposure at the farms, urine samples are collected for 24 hours/day for 4 days. A baseline 24-hour sample is collected before pesticide application. The study is expected to improve exposure assessment in epidemiologic studies of agricultural populations (Baker et al. 2005).

State Biomonitoring Programs

The National Biomonitoring Program, launched in 2001 by CDC, was established to support a variety of state efforts to conduct biomonitoring programs to assist with environmental health tracking at the state level. Thirty-three states received grants in 2002 to initiate biomonitoring program planning. However, only eight of the 33 received grants to implement their biomonitoring plans: New Hampshire, New York, and a consortium of six midwestern states—New Mexico, Arizona, Colorado, Montana, Utah, and Wyoming—known as the Rocky Mountain Biomonitoring Consortium (RMBC).

The New Hampshire Department of Health and Human Services is determining blood mercury concentrations and related freshwater fish consumption, studying speciated arsenic in urine, and analyzing phthalates in urine and PBDEs in serum and breast milk (APHL 2004, 2006). In 2004, New Hampshire received about $300,000 to support its biomonitoring program (APHL 2004).

The New York State Department of Health has developed 10 pilot biomonitoring projects, some of which are completed or under way, includ-

ing the recently completed New York City Health and Nutrition Examination Survey, which includes measurements of mercury, other metals, and cotinine in 2000 adults in New York City; a study of mercury exposure in children in New York City; the New York State Adult Tobacco Survey, which includes an analysis of second-hand smoke exposures; and the New York Angler Cohort Study, which is analyzing exposure to PBDEs and perfluorinated compounds by measuring serum of anglers (Wadsworth Center,[2] unpublished material, September 2003; George Eadon, Wadsworth Center, personal commun., July 26, 2005; APHL 2006). The state is also assessing the possibility of using newborn screening spot blood in future biomonitoring research (APHL 2006).

The RMBC assessed its regional public-health priorities and developed the following nine demonstration projects on the basis of the needs of the community: possible correlation of exposure to arsenic in drinking water and type 2 diabetes, a spot blood metals-analysis feasibility study, health-clinic samples for chemical-terrorism baselines, of relationship between urine arsenic and metal concentrations and drinking-water exposure, assessment of exposure to VOCs from subsurface volatilization, cotinine concentrations associated with environmental tobacco smoke, assessment of exposure to mercury from ingestion of fish, analysis of radionuclides in urine, and biomonitoring of organophosphorus pesticides in urine (Utah Department of Health 2006).

A number of the individual states in the RMBC have initiated biomonitoring efforts. For instance, Arizona has begun a regional arsenic study to determine the relationship between arsenic in drinking water and concentrations detected in urine (APHL 2006). Montana is conducting a regional arsenic assessment similar to that in Arizona (APHL 2006). New Mexico is integrating efforts to identify chemical terrorism through the biomonitoring of thiodyglycol, a metabolite of sulfur mustard (APHL 2006). And Utah is validating methods for biomonitoring of selenium and arsenic (APHL 2006).

In addition to those efforts funded directly by CDC, states have tried to develop biomonitoring initiatives through their state legislatures, including Minnesota (the Healthy Minnesotans Biomonitoring Program, Minnesota Senate Bill 979) and California (Healthy Californians Biomonitoring Program, California Senate Bill 600). State laboratories have also received funding from CDC since 1999 through the Laboratory Network for Chemical Terrorism to develop laboratory capacity to respond to a chemical-terrorism incident. The network supports 62 state, territorial, and metropolitan public-health laboratories in developing capacity to monitor for chemical exposures in blood and urine, including chemical-warfare agents

[2]Derived from New York State Department of Health. 2003. New York State Biomonitoring Program Plan.

and a variety of metals. Participation in the program is designated by three levels of activity:

- Level 3 laboratories actively coordinate with hospitals in clinical-specimen collection, storage, and shipment and work to develop an appropriate response plan (CDC 2006a).
- Level 2 laboratories have the capacity to detect exposures to a number of toxic chemical agents in human blood or urine, including cyanide and metals (CDC 2006b).
- Level 1 laboratories have the capacity to monitor for many chemicals in human blood or urine, including mustard agents and nerve agents (CDC 2006b).

States have been encouraged to apply any "unused capacity" that developed in this program to other biomonitoring projects.

Occupational Biomonitoring Efforts

Of the occupational biomonitoring programs in the United States, two are administered by the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) but implemented primarily at the state level.

The Occupational Safety and Health Standards (29 CFR 1910.1025 [2005]) require employers to collect biomonitoring samples from workers who have been exposed to airborne lead above the current action level of 30 μg/m^3. Employers must have the samples analyzed by laboratories that have met OSHA requirements for blood lead proficiency testing. State health departments often require that increased blood lead results be reported (OSHA 2005).

OSHA also requires biomonitoring of workers for cadmium exposure. Medical surveillance is required for all workers if their urine concentration of cadmium exceeds 3 μg/g creatinine, the Beta-2 microglobulin exceeds 300 μg/g creatinine, or the cadmium in whole blood exceeds 5 μg/liter (29 CFR 1910.1027 [2005]).

In addition to OSHA requirements, NIOSH has initiated the Adult Blood Lead Epidemiology and Surveillance (ABLES) program, a state-based surveillance program of laboratory-reported adult blood lead concentrations (NIOSH 2005). If blood lead is determined to exceed allowable limits, the program includes state interventions: "(1) conducting follow-up interviews with physicians, employers, and workers; (2) investigating work sites; (3) providing technical assistance; (4) providing referrals for consultation and/or enforcement; and (5) developing and disseminating educational materials and outreach programs" (NIOSH 2005). The ABLES program

funds 37 states. Participating states require that laboratories report blood lead concentrations to state health departments (NIOSH 2005).

Private Biomonitoring Efforts

A number of private organizations fund biomonitoring programs for research purposes and to assess exposure at the individual level. The efforts of the American Chemistry Council's Long-Range Research Initiative, the International Life Sciences Institute Health and Environmental Sciences Institute (ILSI-HESI) Biomonitoring Technical Committee, and private laboratories that cater to individual requests to biomonitor for chemicals are highlighted below.

American Chemistry Council's Long-Range Research Initiative

The International Council of Chemical Associations—made up of the American Chemistry Council, the European Chemical Industry Council, and the Japan Chemical Industry Association—is the global coordinator of the Long-Range Research Initiative (LRI), a research program that funds research in the effects of chemicals on human health and the environment (LRI 2001).

One specific subject that LRI solicits and funds research in is characterizing and estimating exposures and interpreting and using biomonitoring data (ACC 2002). Objectives of LRI's biomonitoring program include enabling more accurate application of biomonitoring data to risk assessment, evaluating exposure models and assessments, enabling design of more realistic toxicology tests, providing leadership for governments and other organizations to fund such work, and enhancing the industry's ability to communicate risk (LRI 2005).

Examples of biomonitoring projects that LRI is funding include comparing biomonitoring data with exposure data to interpret ethylene oxide DNA adducts (ethylene oxide bound to DNA) and urine and blood concentrations of benzene metabolites, studying the relationship between phthalate exposure and urinary biomarkers in rats and modeling the relationship for humans, developing and applying more-advanced statistical models to characterize relationships between exposures and biomonitoring data, and evaluating biomarkers of in utero exposures to compare with background concentrations of chemicals (LRI 2001).

International Life Sciences Institute Health and Environmental Sciences Institute Biomonitoring Technical Committee

Although ILSI-HESI is not directly involved in collecting biomonitoring data, it is actively researching their interpretation and potential regulatory

uses. ILSI-HESI supports scientific and educational programs dedicated to health and environmental issues that are of concern to the public, the scientific community, government agencies, and industry. Its Biomonitoring Technical Committee comprises representatives of government, industry, and academe. The technical committee's missions are to delineate the appropriate scientific uses of biomonitoring tools and biomonitoring data needed to characterize exposure to chemicals and to define the criteria for the integration of biomonitoring and toxicology data into a robust risk assessment process (ILSI 2005). The technical committee has a number of working groups that are examining biomonitoring issues, including the application of biologic exposure indices in the occupational vs environmental settings and development of criteria for collecting, applying, and interpreting biomonitoring data. It has convened numerous meetings and workshops, including an International Biomonitoring Workshop in September 2004, which led to a series of case studies of the application of chemical-specific biomonitoring data to risk assessment (Albertini et al. in press; Barr and Angerer in press; Birnbaum and Cohen Hubal in press; Butenhoff et al. in press; Calafat and McKee in press; Hughes in press; Robison and Barr in press).

Private Laboratories

Numerous private laboratories offer biomonitoring services to individual clients. It is difficult to estimate their exact number, but a small sampling of laboratory services has revealed the following. Hundreds of laboratories offer laboratory tests to determine the presence of chemicals in various matrices (blood, urine, and hair). Clients include medical and occupational-health professionals and clinics, academic researchers, attorneys, corporations, and individuals interested in determining personal exposures.

Many of the private laboratories offer screening for heavy metals (including lead, mercury, cadmium, arsenic, aluminum, and nickel) and other chemicals, such as PCBs, chlorinated solvents, trichloroethylene, and pesticides. One such laboratory advertised testing for nearly 70 chemicals. Occupational screening was also offered at some of the laboratories. For many laboratories, people may order test and screening kits over the Internet, by fax, or by telephone. A person can send in a blood, urine, or hair sample for analysis. In some cases, a physician's signature is required to have the sample tested.

Regarding laboratory certification for private laboratories, the Clinical Laboratory Improvement Amendments (CLIA) state the conditions that "all laboratories must meet to be certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988" (57 FR 7139, Feb. 28, 1992). The requirements do not apply to "any

facility or component of a facility that only performs testing for forensic purposes; research laboratories that test human specimens but do not report patient-specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients; or laboratories certified by the Substance Abuse and Mental Health Services Administration (SAMHSA), in which drug testing is performed which meets SAMHSA guidelines and regulations."

Little concrete information is available on the proportion of private biomonitoring laboratories that have attained CLIA certification, but CLIA regulations impose substantial penalties on noncomplying laboratories (CDC 2004). Because proficiency test samples and standard reference materials for analytes not typically measured may be unavailable (CMS 2005), comparability of private-laboratory results with reference ranges developed elsewhere may be open to question.

Biomonitoring Efforts by Environmental Organizations

A number of environmental groups have been actively involved in collecting biomonitoring data in the United States, Canada, and Europe. Those organizations include the Environmental Working Group (EWG), the World Wildlife Fund (WWF), Commonweal, and Environmental Defence (based in Canada). The studies have often been conducted on a smaller scale and with samples from a few people in a select region. Examples are discussed below.

In the United States, EWG has conducted biomonitoring studies ranging from measurement of 287 chemicals in nine volunteers to monitoring specifically for perchlorate in breast milk of women in 18 states (EWG 2003a; EWG 2005). In *Body Burden I*, a study led by Mount Sinai School of Medicine in collaboration with EWG and Commonweal, researchers found an average of 91 chemicals in the blood and urine of nine volunteers. A total of 167 chemicals were identified in the study population (EWG 2003a). A followup study conducted by EWG (*Body Burden II*) in collaboration with Commonweal measured an average of 200 chemicals in cord blood from 10 babies born in August and September 2004. Over 280 chemicals were identified in the samples (EWG 2005). Chemicals tested included perfluorinated chemicals, pesticides, and PBDEs.

In addition to the studies described above, EWG has conducted biomonitoring tests for specific chemicals in breast milk, such as PBDEs (EWG 2003b).

Commonweal has conducted biomonitoring studies, primarily in Californians. *Taking It All In—Documenting Chemical Pollution in Californians Through Biomonitoring* (Commonweal 2005) monitored for 25 chemicals in six categories: mercury, organochlorine pesticides, perfluori-

nated compounds, PBDEs, bisphenol A, and phthalates in 11 people (Commonweal 2005).

Environmental Defence recently released *Toxic Nation: A Report on Pollution in Canadians* (Environmental Defence 2005). Samples were collected from 11 people for the presence of 88 chemicals, including heavy metals, PBDEs, PCBs, perfluorinated chemicals, organochlorine pesticides, organophosphorus-insecticide metabolites, and VOCs. The study objectives included determining whether pollutants were present at measurable concentrations in Canadians, identifying chemicals of concern, and creating public awareness of methods for avoiding exposure.

WWF has conducted similar biomonitoring studies in a cross-section of the population in the UK. As reported in *ContamiNation*, WWF took samples from 155 volunteers in 13 locations in England, Northern Ireland, Scotland and Wales and monitored for 12 organochlorine pesticides, 45 PCB congeners, and 21 PBDEs (WWF 2003).

In a similar survey (*Bad Blood? A Survey of Chemicals in the Blood of European Ministers*), WWF collected samples from 14 government ministers of 13 EU countries and analyzed them for 103 chemicals, including organochlorine pesticides, PCBs, synthetic musks, perfluorinated chemicals, PBDEs, phthalates, and antibacterials (WWF 2004).

INTERNATIONAL BIOMONITORING EFFORTS

Many biomonitoring studies are undertaken outside the United States, primarily in Europe. The more comprehensive efforts have been administered through the Science, Children, Awareness-Raising, Legal Instruments and Evaluation (SCALE) program, the World Health Organization, and a variety of programs in Germany, Portugal, and Belgium. (See Table 2-1 for more details on examples of biomonitoring efforts at the international level.)

Of the European studies reviewed, many measured heavy metals, cotinine, PCBs, pesticides, PAHs, dioxins, phthalates, and VOCs. Germany has taken a substantial lead in this respect through its comprehensive population-based surveys (German Environment Surveys) and concerted efforts to develop health-protective reference values for the general population. In addition European countries have been actively involved in occupational biomonitoring efforts. In fact, some countries have biomonitoring surveillance programs that have been required by law.

Science, Children, Awareness-Raising, Legal Instruments and Evaluation

Recent efforts to coordinate research and develop a "coherent approach" to biomonitoring across the European Union (EU) have led to the inception of the SCALE program (European Commission 2004). SCALE is part of a

larger European Environment and Health strategy to reduce and prevent diseases related to environmental exposures, with emphasis on exposures of susceptible populations, including children (Commission of the European Communities 2004). An initial survey conducted by SCALE of biomonitoring efforts focusing primarily on children's exposures identified nearly 100 efforts in the EU alone, this is a preliminary effort that is being continuously updated (European Commission 2004). Nineteen projects currently examine exposures to dioxin and PCBs; 42 heavy metals; and 25 asthma or allergies (European Commission 2004). Several EU studies of exposures of children incorporated prenatal and postnatal exposures and markers of effect and susceptibility (European Commission 2004; Neri et al. 2006).

The strategy includes planning for a European Integrated Environment and Health Monitoring and Response System, which involves establishing a European Union Biomonitoring Framework that is to "assess environment and health linkages relative to children and to generate appropriate policy responses." The strategy also addresses the need for better coordination among European biomonitoring initiatives.

The EU has developed a pilot project in an effort to coordinate biomonitoring approaches and encourage the sharing of methodologies among member states. The pilot project will test the hypothesis that human biomonitoring can be performed in a comparable way throughout Europe and that such a coordinated approach will provide better information on the relationship between health effects and exposure information. The aim of the pilot project is to establish reference values and identify reference ranges for specific biomarkers, and to evaluate the effect of policy measures if biomonitoring data are collected over time. The pilot project may elucidate the need for a full-scale European biomonitoring program, which will include harmonized procedures and comparable biomonitoring protocols (ESBIO 2006).

World Health Organization

WHO has conducted three international studies of PCBs, polychlorinated dibenzodioxins, and polychlorinated dibenzo-furans in human milk during 1987-2003 (WHO 2000). The first two surveys were conducted in 1987-1988 and 1992-1993 in a number of European countries. The third, conducted in 2000-2003, included additional countries. A fourth survey has been developed with the intent to assess the persistent organic pollutants (POPs) found in human milk so that each country can better identify and set priorities among POPs for remedial action (WHO 2000). The sample population will include at least 50 mothers from each country who are planning to breastfeed (WHO 2005). Two sampling periods have been proposed, the first to obtain a baseline sample of POPs in representative

individual and pooled samples of human milk, the second to include similarly selected participants after a 4-year period (WHO 2005).

Germany

Germany has comprehensive occupational and population-based biomonitoring programs. The German Environmental Surveys (GerESs) are a multistage probability sample of the German population that include analysis of tissues for traces of environmental chemicals (see Table 2-1 for analytes measured) (Becker et al. 2003). The surveys were conducted in 1985-1986 (GerESI), 1990-1992 (GerESII), and 1998 (GerESIII) and included 4,822 people 18-69 years old (Becker et al. 2003). The most recent survey, GerESIV (2003-2006), will include 1,800 children in 150 sampling locations (GerES 2005). Beginning in 1993, data from the GerES surveys and other epidemiologic and toxicologic studies were used to establish reference values and human biological monitoring (HBM) values (GerES 2005).

Reference values "indicate the upper margin of the current background exposure of the general population and [are used] to identify subjects with an increased level of exposure" (Jakubowski and Trzcinka-Ochocka 2005) compared with the background population level. Those values are derived from data on blood, urine, and other tissues collected from population studies (Ewers et al. 1999). Reference values may be derived differently for susceptible groups if physiologic differences are substantial (for example, children vs adults) (Ewers et al. 1999).

HBM values are derived from toxicologic and human studies and are health based (Jakubowski and Trzcinka-Ochocka 2005). Two types of HBM values exist: HBM I, "the concentration of an environmental toxin in human biological material below which there is no risk of adverse health effects"; and HBM II, "the concentration above which there is an increased risk of adverse health effects in susceptible individuals in the general population" (Jakubowski and Trzcinka-Ochocka 2005). An HBM I value serves as an alert level, and an HBM II value is an action level at which immediate efforts should be made to reduce exposure and further clinical examination should follow (Ewers et al. 1999). HBM values and reference values have been derived for a number of chemicals, including lead, cadmium, mercury, pentachlorophenol (PCP), and arsenic.

Additional examples of European biomonitoring efforts are included in Table 2-1.

HUMAN-SPECIMEN BANKING

Lee et al. (1995) defined environmental-specimen banking as "a long-term, stable storage of specimens sampled from the physical environment,

such as air, water, soil, or sediment samples, or of biological specimens sampled from human, animal, or plant populations." If collected and stored appropriately, tissues from specimen banks can be used in retrospective and prospective cohort studies (Zenick and Griffith 1995). That allows the testing of hypotheses as the scientific community identifies them after sampling has taken place. Ideally, data provided from stored-specimen banks can be used to "relate levels of environmental contamination to health outcomes via doses" (Holzman 1996).

There are a number of large specimen banks and repositories in the United States, administered primarily by federal government. Others are administered by the military, universities, corporations, and nonprofit organizations (NBAC 1999). Similarly, the EU has specimen banks available for research purposes. A few examples from in the United States and EU are described below.

In the United States, CDC has been involved in tissue and specimen banking primarily to provide information for use in epidemiologic studies and research programs. Two larger-scale programs include specimens from NHANES and the Agency for Toxic Substances and Disease Registry (ATSDR) Specimen and Data Repository.

Regarding storage of tissue resulting from NHANES, serum, plasma, and urine have been collected and stored for future research projects. Specimens from NHANES III and NHANES 1999-2004 are available. Projected uses of the specimens include developing new analytic technologies, identifying new biomarkers, and intramural and extramural research, as approved by CDC (Gunter 1997; NCHS 2005).

In 1995, ATSDR funded the CDC-ATSDR Specimen and Data Repository to store over 6 million biologic specimens for use in various research work (Gunter 1997). Numerous specimens are stored in the repository, including serum, cells, and tissues. The repository was designed to handle a large portion of CDC's biologic specimens (Gunter 1997).

The EU, through its Health and Environment Strategy, has stressed the importance of increased funding and capacity in addition to improved coordination among current biobanking activities (European Commission 2004). A number of European countries have established national specimen banks, including Germany and Sweden.

The German Environmental Specimen Bank, initiated in 1985, annually samples and archives specimens to determine the effectiveness of environmental regulations and to conduct retrospective monitoring (European Commission 2004). The bank collects six types of human specimens—whole blood, blood plasma, scalp hair, pubic hair, saliva, and 24-hour urine samples from people 20-29 years old in four cities (Münster, Halle/Saale, Greifswald, and Ulm). Screening is conducted to determine the pres-

ence of a variety of metals, PCBs, hexachlorobenzene, PBDEs, phthalates, and PCPs (European Commission 2004).

The Swedish Environmental Specimen Bank is a centralized storage bank that has been operational for 20 years. It conducts annual sampling of a variety of environmental and human specimens for use in a number of studies, including retrospective analyses. Regional banks store human blood for use in these studies (European Commission 2004).

The European Prospective Investigation into Cancer and Nutrition (EPIC) is the largest study of diet and health in the EU, with over 520,000 participants in 10 European countries. The study, initiated in 1992, collects detailed information and diet and lifestyle factors in addition to blood samples, which are stored for future analyses. The study participants will be followed for the next 10 years to investigate the role of nutrition in the development of chronic disease (IARC 2005).

UK Biobank is a long-term human-specimen bank that will be initiated at full scale in 2006, although pilot projects are under way. The project will collect information, including blood (fractioned to plasma or serum) and urine samples, from 500,000 participants 40-69 years old. The study will follow participants over 20-30 years to study progression of chronic diseases.

Supporting the efforts described above, the International Society for Biological and Environmental Repositories was founded in 2000 to provide guidance on repository management, disseminate information regarding the effective management of specimen collections, and develop efforts to educate the community about related issues (ISBER 2005).

Additional information about biobanking is presented in Table 2-1 and in Chapter 4.

GENERAL OBSERVATIONS

A review of large-scale biomonitoring programs in the United States and the EU did not reveal substantial differences in the types and number of analytes measured (see Table 2-1 for discussion of examples of studies). Most studies included monitoring of heavy metals (often lead and mercury), pesticides, PAHs, PCBs, dioxins, phthalates, VOCs, and emerging chemicals (perfluorinated compounds and PBDEs).

Regarding funding, the Government Accountability Office, in its review of the long-term strategy for monitoring of exposure to chemicals in the United States, noted that, "as compared to the hundreds of millions spent on monitoring contaminants in environmental media, we estimate that $7 million was spent collectively by CDC (including ATSDR) and EPA on their respective human exposure efforts in 1999" (GAO 2000). Although funding for such efforts in the United States has increased with the

CDC *National Reports on Human Exposure to Environmental Chemicals* and NHANES, state biomonitoring efforts have not fared as well. For instance, funding for implementation of state biomonitoring plans has been in place in only three states or regions as of 2004. In addition, although the state planning grants were funded at $5,000,000 and $4,970,500 in FY 2002 and FY 2003, respectively, only $2,650,000 was allotted for implementation (APHL 2004). The NCS, would provide a valuable database of children's exposures; however, its funding status is currently being debated. The burden of collecting biomonitoring data seems to fall on CDC.

Without state and local programs, valuable geographic and temporal differences in exposure cannot be examined. States are better able to target programs to serve the needs of the communities and may be able to incorporate environmental sampling to augment human monitoring data (Needham et al. 2005a). Thus, increased funding for state programs should have a high priority; as stated by the NY Wadsworth Center, a CDC grantee, "significantly higher funding is needed to support larger biomonitoring exposure investigations, ability to respond to new public health issues, and to participate in external collaborations to address emerging problems" (Wadsworth Center, unpublished material,[3] September 2003; George Eadon, Wadsworth Center, personal commun., July 26, 2005).

An assessment of biomonitoring efforts reveals that the biomonitoring of chemicals in children seems to have a high priority in both the United States and the EU, as evidenced by the sheer number of programs and the aggressive agenda for future monitoring of this population.

Other issues include the monitoring of susceptible populations in the United States and Europe. In addition to current population-based biomonitoring programs, future U.S. efforts should include biomonitoring of populations that may be at higher risk of exposure to chemicals. Additional funding for state or local biomonitoring programs may provide an opportunity to evaluate exposure of those populations (for example, state HANES).

As discussed in this chapter, because biomonitoring is being conducted on an international level by numerous organizations, and there is much knowledge to be gained from understanding patterns of exposure worldwide, the committee encourages the exchange of biomonitoring information and expertise globally. This includes sharing biomonitoring data, study approaches, and tracking of trends. Such coordination will enhance national and international standardization and validation of biomonitoring techniques and provide for complementary study designs. To this end, the committee encourages the development of such information exchanges be-

[3]Derived from New York State Department of Health. 2003. New York State Biomonitoring Program Plan.

tween EPA and the Organization for Economic Co-operation and Development (OECD).

CONCLUSIONS

An assessment of current U.S. and European biomonitoring efforts has yielded the following conclusions:

- Biomonitoring is rapidly developing in the United States and Europe with comparable types and numbers of analytes being measured.
- The biomonitoring of chemicals in children appears to have a high priority in both the United States and the European Union.
- State and local biomonitoring programs have the potential to provide valuable biomonitoring data on the geographic and temporal differences in exposure among populations. Increased funding for such efforts in the United States is needed.

RECOMMENDATIONS

- The committee recommends that additional funding be committed to state-level biomonitoring programs.
- The committee encourages the sharing of biomonitoring data between the EPA and the OECD to foster international collaboration and develop the field of biomonitoring.

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3

Framework to Characterize Biomarkers and Uses of Biomonitoring

RATIONALE FOR A FRAMEWORK TO CHARACTERIZE BIOMARKERS

The pace at which developments of biomarkers occur tends to exceed the biomonitoring community's ability to cope with its obligations to ensure proper transmission of information on the meaning of the measurements. There are increasing anecdotal stories in the mass media about the concerns of people whose blood has been found to contain more than 100 chemicals. But the fact is that the numbers of studies, subjects, and substances determined in human biomonitoring are increasing (e.g., National Health and Nutrition Examination Survey), as is the awareness of the general public of those chemicals in our bodies (e.g., Sexton et al. 2004). Consequently, there is a need for clarification of what biomarkers can and cannot be used for. Despite proper warnings to the effect that "the measurement of an environmental chemical in a person's blood or urine does not by itself mean the chemical causes disease" (CDC 2005), people who have almost unlimited access to good and bad information about chemicals no longer appear satisfied with such general words of caution. Not only is the general population entitled to know the advantages and limitations of biomonitoring, but those with public-health responsibilities also need to be adequately informed. The correct interpretation of biomarker measurements is therefore of utmost importance.

In many cases, data on biomarkers are obtained with the sole purpose of collecting information about their background concentrations in the

general population, not to assess health risks associated with the measurements. As will be discussed in later chapters, such studies are laudable in that they contribute to our knowledge about human exposure to environmental chemicals. But the limitations of that type of information are not necessarily recognized by all who need to know and understand them. The committee considered that clarification of the properties of the various biomarkers of exposure would be useful in helping to understand and clarify what can be said about a given measurement. A systematic framework to characterize the properties of biomarkers would help to inform scientists and the general population about biomarkers and their meaning when they are used in biomonitoring studies. It would also allow assessment of potential research gaps that need to be addressed to meet the requirements of specific uses of biomarkers. Detailed information about the interpretation of biomonitoring data is provided in Chapter 5. The present chapter focuses on the properties that characterize biomarkers of exposure in general. These properties are based on a weight-of-evidence approach that takes into account the specific context of a biomonitoring study under consideration.

TYPES OF BIOMARKERS

Chapter 1 describes the relationship between exposure to a toxic chemical and its clinically relevant health effects as a series of steps along a continuum. There often is no clear-cut distinction between some of the steps, and Figure 1-1 can help position three types of biomarkers: biomarkers of exposure, of effect, and of susceptibility.

As the name implies, biomarkers of exposure allow assessment of exposure to a chemical on the basis of its measurement in a biologic matrix (NRC 1991). Typical examples are the measurement of dioxins in blood or blood lipids, mercury in hair, benzene in exhaled breath, and cadmium in urine. In itself, quantification of such a biomarker in a biologic matrix proves only that the chemical is in the organism. If the substance is not otherwise known to be endogenous, it can be concluded that there has been a transfer from the external environment to the individual organism. Any further interpretation of the concentration of a biomarker of exposure requires additional information about some of the relationships in the continuum. If the biomarker of exposure indicates that a chemical reached a critical target in the organism—for example, if it formed a DNA adduct—there is a greater likelihood of a potential link with a biological perturbation. As discussed in Chapter 1, this report focuses on biomarkers of exposure.

Biomarkers of effect are used to assess changes that have occurred in the biochemical or physiologic makeup of an individual. The further to the right in the continuum the biomarker is, the greater the clinical or health

relevance of its measurement. An abnormal value of a biomarker of effect near the center of the continuum may not signal detrimental effects on the health of an individual or group if, for example, the perturbation is reversible and steps are taken to ensure that the exposure that caused it ceases. However, the abnormal value can serve as a trigger for a remedial action. Examples of biomarkers of effect are plasma cholinesterase activity, urinary β_2-microglobulin, and packed red-cell volume (hematocrit).

The passage from one step to the next along the continuum will often depend on a person's characteristics. A biomarker that allows the assessment of a person's susceptibility to alter the progression along the continuum is called a biomarker of susceptibility. Examples are enzymatic genotypes and phenotypes, such as those seen with glutathione-S-transferase M, a phase II conjugation enzyme that often contributes to the detoxification of some electrophilic compounds (Perbellini et al. 2002).

KEY USES OF BIOMONITORING DATA

Biomonitoring has been a key tool in some landmark public-health actions. The incentive to reduce collective exposure to lead and thereby to protect the public in general and children, who are more sensitive to its deleterious neurotoxic effects, would probably have been less if we had not known how much lead was reaching our bodies and how much lead in our bodies was problematic. Just as important, the prospective followup and monitoring of blood lead clearly illustrated that our exposure-reduction strategies were successful in lowering it (Pirkle et al. 1995). The lead case is developed further in Chapter 5. The determination of aflatoxin-derived DNA adducts was also a key step in increasing our understanding of the carcinogenic effect of this naturally occurring toxin. It allowed us to derive a quantitative risk assessment of its hepatocarcinogenicity, which guided exposure reduction (Sharma and Farmer 2004). More recently, the measurement of biomarkers of exposure to methyl parathion was instrumental in understanding local epidemics of poisoning with this insecticide and in establishing remediation strategies (Rubin et al. 2002). The once unthinkable efforts to reduce exposure to second-hand smoke were proved successful through the Centers for Disease Control and Prevention (CDC) *National Reports on Human Exposure to Environmental Chemicals*. Indeed, from 1988 to 2002, a 68% reduction in urinary concentrations of cotinine (a specific biomarker of exposure to nicotine) was demonstrated in children 4-11 years old (Sinks 2005). Without specific measurements, the actual dose resulting from second-hand smoke would have been only inferred from expensive external measurements of airborne nicotine from cigarette smoke. The indirect assessment might also have been considered merely conjectural and unproved. But the unambiguous demonstration that it was

an important pathway of exposure to chemicals contained in tobacco smoke and that control policies reduced exposure was a key step in the success of the public-health strategy related to smoking (active and passive). Some argue strongly that public-health professionals and clinicians would benefit from access to a large pool of well-characterized biomarkers to guide both prevention of adverse health effects and health promotion (Jackson 2005).

Biomonitoring can also serve as a valuable tool in various public-health activities aimed at avoiding the deleterious effects associated with exposure to toxic substances. From a risk-assessment and risk-management perspective, the determination of markers of internal exposure may serve a number of purposes that can be situated along a continuum of risk-assessment and -management activities (e.g., Burke et al. 1992). Four broad categories are represented here because they pertain to activities that use biomonitoring: scoping, status and trends, exposure and health research, and risk assessment. Examples of types of activities included in each category are listed in Box 3-1. Scoping is a basic risk-management activity that may provide the first indication of a potential problem. The qualitative information gathered through scoping assists in addressing fundamental questions such as, is a chemical present in the biomonitoring sample (Burke et al. 1992)? Examples of scoping include screening, exploratory and source investigations,

BOX 3-1
Continuum of Risk-Assessment and -Management Activities Related to Exposure Biomonitoring

- Scoping
  - Screening
  - Exploratory investigations
  - Source investigations
  - Societal-hazard identification
- Status and Trends
  - Exposure surveillance
  - Population research
  - Pathway research
  - Decision validation and health surveillance
- Exposure and Health Research
  - Epidemiologic research (ecologic and analytic)
  - Toxicologic research
  - Pharmacokinetic and pharmacodynamic research
  - Community and occupational investigations
- Risk Assessment
  - Population risk characterization
  - Clinical applications
  - Individual risk characterization

and societal hazard identification. Status and trends provide an assessment of the concentration of chemical in the population (for example, blood or urine) and whether the concentration of the chemical may be varying over time, across geographic regions, or within populations. Information on status and trends can assist with population surveillance and research. The biomonitoring data may be utilized to assess potential sources of exposure when combined with pathways research. Biomonitoring data can be used to support exposure and health research. Population-based biomonitoring data used in epidemiologic studies can identify highly exposed subpopulations and health endpoints of concern. This in turn can be applied to community and occupational studies. The data can also identify information needs for toxicologic, pharmacokinetic, and pharmacodynamic research. Biomonitoring data can be applied in clinical evaluations (that is, childhood lead) to assess individual risks or exposure.

All those activities have specific purposes and may be conducted alone (for example, for priority-setting among public-health actions) or as parts of a multitier strategy. Links between risk-assessment and -management activities (why biomonitoring is conducted) and the properties of the biomarkers (what characteristics our biomonitoring tools need to have for us to be able to conduct these activities) will be presented below.

PROPERTIES OF AND GROUPING FRAMEWORK FOR BIOMARKERS OF EXPOSURE

A simplified version of the relationships described in the continuum presented in Figure 1-1 shows the links between external dose,[1] internal dose, and biologic effects as a triangle (Figure 3-1). The diagram illustrates the "operational" relationships between these elements, not the biologic relationships. Indeed, a systemic toxicant has to penetrate the organism before exerting its action. The direct link between external dose and biologic effect has no toxicologic meaning itself, but, as will be discussed below, more published information is available on the relationship between the external dose of toxicants and their biologic effects than between the internal dose—as assessed by a biomarker measurement—and biologic effects. The interpretation of biomonitoring data, and thus possible key uses, will depend on the body of knowledge about these links from animal or human studies.

[1]External dose, as used in the report, refers to the amount of chemical that is inhaled, is ingested, or comes in dermal contact and is available for systemic absorption. External dose is typically expressed in units of milligrams of chemical per kilogram of body weight per day (mg/kg/day).

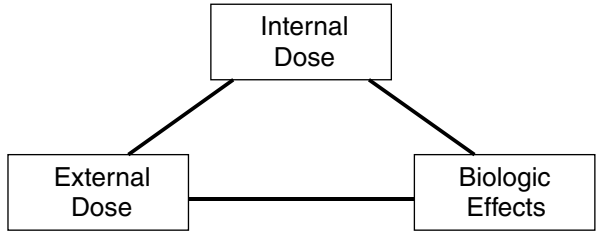

FIGURE 3-1 Operational relationships between internal dose, external dose, and biologic effects. Internal dose is measured through biomonitoring. Source: Adapted from Bernard and Lauwerys 1986.

Ultimately, a biomarker of exposure for which all the relationships in Figure 3-1 have been clearly delineated will probably be useful for risk-assessment purposes. The validation of biomarkers of exposure useful for risk-assessment purposes has been described (Schulte and Talaska 1995; Dor et al. 1999; WHO 2001). Chapter 5 provides case studies to illustrate how even partial knowledge of the relationships can guide various risk-assessment activities. But outside the complete risk-assessment framework, it should be stressed that even when only partial information is available, a biomarker can be useful from a public-health perspective for conducting some of the activities presented in Box 3-1. For example, observation in a prospective study that the concentration of a biomarker is increasing in the population might trigger complementary studies to understand the origin of exposure and its potential deleterious effects if these are unknown.

As indicated above, the body of knowledge about a given biomarker of exposure can be variable, and the interpretation of a biomarker concentration will depend on this body of knowledge. A framework (see Table 3-1) to characterize biomarkers was therefore developed to help the users of biomarkers to understand the advantages and the limits of interpretation of biomarker results. The framework links the potential uses of biomarkers to their properties. It is based on the simplified relationships between external dose, internal dose, and biologic effects (Figure 3-1). Table 3-1 consists of a matrix, the row headings are the properties of the biomarkers, and the column headings are the grouping categories (I through VII) to which specific biomarkers might belong, depending on their properties. Based on the properties of a biomarker for a specific grouping category, the biomarker provides information for the internal dose, external dose, or biological effects of a particular chemical, thus providing information on uses of the biomarker. The matrix indicates the minimal properties of a biomarker for inclusion in one of the groups indicated.

TABLE 3-1 Framework for Grouping Biomarkers of Exposure[a]

		Biomarker Group						
Properties of Biomarkers		I	II	III	IV	V	VI	VII
Reproducible sampling and analytic method			R	R	R	R	R	R
Known relationship of external dose to [BM] in animals[b]				R				
Known relationship of external dose to [BM] in humans[b]					R		R	R
Known relationship of [BM] to biologic effect in animals							O	
Known relationship of [BM] to biologic effect in humans						R		R
Known relationship of external dose to response in animals							O	
Known relationship of external dose to response in humans							O	
Biomarker informs about	Internal dose		√	√	√	√	√	√
	External dose[c]			√	√		√	√
	Biologic effects[d]					√	√	√
						Potential for risk assessment		

[a]Checkmark in lower portion of table means that biomarkers in group can inform about stated elements of dose and effect.
[b]Implies knowledge of pharmacokinetics of biomarker in relation to exposure to parent chemical.
[c]The relationship between external dose and internal dose may be influenced by metabolic polymorphisms and other factors, including socioeconomic status and racial and ethnic differences.
[d]Biologic effects may include a wide range of observations, from very early biochemical perturbations to clinical signs of alteration of health.
Abbreviations: [BM] = concentration of biomarker; R = required: O = optional (at least one of these is required).

Determining which properties are present in connection with a given biomarker should be based on a weight-of-evidence approach (Krimsky 2005) and will be peculiar to the context in which the biomarker is intended to be used. For example, there could be studies relating the concentration of a biomarker to toxic end points in workers exposed to relatively high doses of a toxicant. But the measured end point could be irrelevant for the general population exposed to doses that are much smaller (see "Adapting Occupational Reference Values to the General Population" in Chapter 5). In such a case, a toxicologist might consider that the biomarker does not possess the property "known relationship of [BM] to biologic effect relationship in humans" (where [BM] is the concentration of the biomarker) for the purpose of a study of the general population. In other words, professional judgment remains at the core of the application of the framework. Because each of the various risk-assessment and -management activities described in Box 3-1 may have its own specific purpose, a biomarker with a low group number may be just as valuable as one with a high number, given the objectives for which it is used.

The examples provided below of biomarkers in the various groups are presented for illustration purposes only and should not be considered as a final committee judgment on the group to which a given biomarker belongs. Readers interested in a more detailed discussion of some of these examples should consult Chapter 5.

Group I biomarkers correspond to substances that have been observed in bodily fluids but for which no relationships described in Figure 3-1 have yet been characterized. Even the analytic methods have not been shown to meet the basic criteria described in Chapter 4. Biomarkers in this category may be considered useless, but they might still find some utility in case of a sudden major accidental spill or intentional contamination with a given chemical. Indeed, suggestive evidence that a substance has the potential to cross the biologic barriers and find its way into the body may be important information. Any results with this type of biomarker must be viewed with caution because one may not be certain of chemical identity, quantitative accuracy, or biomarker specificity (for example, its presence in bodily fluids may be due to endogenous or other exogenous sources). Group I biomarkers can also include quantitatively important chromatographic peaks corresponding to uncharacterized substances and be found fortuitously during analyses of other well-characterized substances. The latter observations might trigger more research to identify the chemicals and understand their origin in the analyzed biologic sample. Various scoping activities can be pursued with such biomarkers. While this approach is not typically used in population biomonitoring studies, the finding of hundreds of unidentified peaks in human adipose tissue potentially of xenobiotic origin (Thornton et al. 2002), suggests that such an approach may be warranted. The field of

forensic toxicology provides examples where unknown peaks are investigated and shown to be related to human overdose or toxicity, with their identification leading to the development of important Group I (or higher) biomarkers (Broussard et al. 1997; Broussard et al. 2000).

Group II biomarkers also have not been linked to external exposure or to biologic effects, but sampling and analytic methods have been shown to yield reproducible and reliable results. Achieving this laboratory validation is a natural next step after the mere observation and identification of a chemical in human body fluids. It means that competent laboratories in different parts of a country or in different countries can obtain similar results. At the scoping stage of the risk-assessment and -management activities, for example, this implies that observations from different geographic locations—or samples collected at different times—can be reliably compared. From that perspective, status and trend activities can also be undertaken with such biomarkers. It should be noted, however, that the results still cannot be interpreted from a risk-assessment or clinical perspective. Moreover, because no link with external exposure to this substance or its parent compound has yet been established, this type of biomarker cannot guide pathway analyses or remedial actions. Polybrominated diphenyl ethers (PBDE) are illustrative of this group. Indeed, at the time of publication of this report, PBDEs could be measured reliably in human blood, but there is insufficient information to establish a relationship between the measurements and either external dose or toxicity. Developing such relationships is important, given the preliminary evidence of hormonal and developmental effects of PBDEs (Birnbaum and Staskal 2004).

With group III biomarkers, a reliable sampling and analytic technology is available, and a relationship between the external dose and the concentration of the biomarkers in laboratory animals has been demonstrated. The latter is important additional information in that it increases one's confidence, when using information on such biomarkers, that the greater the concentration of the biomarker, the greater the dose received. However, because the information is available only from animal studies, an external dose to humans cannot be inferred from biomarker concentration information. Because no information is available on the human bioavailability of the parent chemical for various exposure routes, as with group II biomarkers, that limits the utility of group III biomarkers in guiding pathway analysis. Sometimes, good pharmacokinetic models are available to describe the fate of the substance in animals and some of the key parameters of the model are known for humans or can be inferred with reasonable confidence. Under such circumstances, the utility of group III biomarkers can expand to that described for the next group, group IV.

Group IV biomarkers also can be sampled and analyzed with reliable methods. In addition, the relationship between external dose and biomarker

concentration has been established in humans. That can stem, for example, from pharmacokinetic studies of human volunteers, from occupational studies of workers whose exposures have a much larger range than that encountered in the general population, from case studies of accidental poisoning, and from community studies in which multimedia exposure has been carefully analyzed. Ideally, the pharmacokinetic behavior of the parent chemical and of the biomarker is characterized on the basis of various exposure pathways, such as inhalation, ingestion, and dermal exposure. Such risk-assessment and -management activities as scoping, status and trends, and, to some degree, exposure and health research can be conducted using biomarkers in this group. Even without adequate knowledge about the toxicity of the substances involved, remedial actions can be taken to reduce exposure if the pathways that lead to the presence of the biomarker are well defined; however, this will typically not be available from human pharmacokinetic studies and would require robust exposure assessment as part of the establishment of a dose-biomarker relationship.

Because information is available about the toxicity of the parent chemicals of group V, VI, and VII biomarkers or of the biomarkers themselves, these biomarkers potentially have properties that allow their use for risk-assessment purposes.

For group V biomarkers, the relationship between concentration—internal dose—and the toxicity of the parent chemical has been established and it is therefore usually possible to determine a biomarker concentration below which no toxicity is observed. Consequently, it is possible to predict the likelihood of toxicity associated with the parent chemical in a person or in a community. Of course, such factors as the specificity of the biomarker (whether it is peculiar to a given parent chemical or common to other substances) have to be taken into account when interpreting results. When test results obtained concomitantly indicate biologic anomalies or disease, group V biomarkers may help to establish whether there is a plausible causal relationship between the abnormal test results and exposure to the parent chemical. Most risk-assessment and -management activities along the continuum shown in Box 3-1 can be conducted, with augmentation if an exposure assessment showing major sources of human exposure to the chemical is available. That would enable apportionment of exposure and development of intervention measures if deemed necessary on the basis of the biomonitored concentrations found and the risks they imply. Group V is the first group in this framework that allows risk assessment to be performed on the basis of available data.

Group VI biomarkers have the same fundamental properties as those in group IV, so they also share basic uses. But group VI has another important attribute: toxicity information is available. It could be the dose-response relationship with the parent chemical in animals or in humans or the rela-

tionship between the biomarker concentration (the internal dose) and the toxicity that is known from animal studies. Such biomarkers can therefore inform the investigator about internal dose, external dose, and biologic effects (the three elements of the triangle presented in Figure 3-1). Uses of such biomarkers span all risk-assessment and -management activities. Many urinary phthalates probably belong to this group in that much is known about phthalate toxicology in animals and there is new information relating biomarker levels to possible effects in humans (Swan et al. 2005).

Group VII biomarkers can also be useful in risk assessment. Compared with group VI, the hallmark of group VII is that all operational relationships described in Figure 3-1 have been established in humans. The major improvement in group VII, compared with group V, is that one can now determine how changes in intake dose will affect biomarker concentrations; this can facilitate intervention decisions. However, as pointed out above, interventions are possible even without knowing the relationship between external dose and biomarker concentration as long as pathway analysis can document the major sources of chemical intake. There would probably be a consensus that blood lead belongs to group VII.

The committee believes that this framework will facilitate the dialogue between all interested and affected parties around biomonitoring, but competent professional judgment will remain at the core of the biomonitoring activities used in risk-assessment and -management. The depth of scientific knowledge can be very different between two biomarkers in the same group, but the framework assumes that enough is known to meet the qualifying properties shown in Table 3-1. And it is probably important to emphasize that with a given toxicologic database on any biomarker and its parent chemical, a weight-of-evidence approach will not necessarily lead all toxicologists to the same conclusion regarding the group to which a biomarker belongs. There would consequently not necessarily be a consensus on the interpretation of the biomonitoring results. However, it is hoped that the framework crystallizes the scientific debate over specific issues, enough to help in achieving such a consensus. Additional information, such as the half-life and other metabolic properties of a given biomarker, will determine the conditions under which the framework can be used for an intended purpose. The committee considers that biomarker selection should account for metabolism and be both biologically significant and relevant to the outcomes of concern. For example, a cross-sectional survey based on a single measurement of a rapidly metabolized chemical may provide limited or even misleading information concerning true population exposure levels. Although half-life, metabolic properties (which may be influenced by genetic polymorphisms or other lifestyle factors—see Chapter 4), and metabolites are key considerations, the committee intentionally did not factor metabolism into Table 3-1, as biomarkers with very different rates of metabolism may have similar applications.

The framework allows researchers and public-health authorities to select a biomarker on the basis of "standard" toxicologic properties depending on the objective of an investigation. It also helps to delineate the limits of some types of biomarkers and, we hope, to communicate information about biomarkers to the general public better. For example, a group II biomarker would be the quintessence of the CDC statement that the presence of a biomarker "does not by itself mean the chemical causes disease." It is important to understand that a group VII biomarker is not necessarily better than a group IV biomarker, because the appropriate selection will rest on the intended purpose of its use along the continuum of risk-assessment and -management activities described in Box 3-1. Hence, there should be no a priori necessity to make all biomarkers group VII biomarkers.

It is outside the scope of this report to establish the group to which every existing biomarker of exposure belongs according to the framework presented. Furthermore, the group designation has to be contextualized to a study's objectives, as stated previously. Some case studies will be presented in Chapter 5, however, to illustrate the potential usefulness of the framework.

CONCLUSIONS

- A systematic framework to characterize the properties of biomarkers is a means of informing scientists and helps to inform the general population about biomarkers and their use in biomonitoring studies. It also allows an assessment of research gaps that need to be addressed to meet the requirements of some specific uses.

RECOMMENDATIONS

- Investigators should use the proposed framework as a guide to characterize the biomarkers they intend to use in a biomonitoring study. The framework might serve as a guide in interpreting the results of the studies and in communicating the study objectives to various audiences.
- The grouping framework should be used to specify the objectives of research projects in the development and validation of various biomarkers, that is, which properties of the biomarkers will be examined and how the studies may contribute in repositioning the biomarker in the framework.
- Biomonitoring study design should consider absorption, distribution, metabolism, and elimination in selection of appropriate biomarkers to address the goals of research and surveillance.

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4

Considerations in the Design of Biomonitoring Studies

In Chapter 3, the committee delineated a diverse array of uses to which biomonitoring studies are or will foreseeably be put to use (Box 3-1). Detailed discussion of the scientific approaches for each of them is beyond the scope of this report, but there are some issues in the design, conduct, and analysis of *all* biomonitoring studies for which the committee deemed review of scientific practice crucial to the further development of the field. The committee addresses these issues in this chapter.

Although the need for attention to scientific rigor attends every emerging technology in biomedical and environmental health science, and is thus not peculiar to biomonitoring, some aspects of biomonitoring demand special attention:

- In developing biomarkers, there are no "gold standards" against which a result or finding can be readily evaluated; in most cases, biomonitoring will afford the first opportunity for scientists to assess even qualitatively the extent to which humans are exposed to, absorb, and might be harmed by innumerable contaminants of the human-made and natural environment.
- Measured concentrations of biomarkers are often extremely low (in the 1 part per billion range or below) and subject to highly uncertain causes of variation, such as individual genetic differences, age, diet, habits, weather conditions, time of day, recent activity, medication and illness, and other exposures.

- Compared with measures of contaminants in air, water, or food, biomonitoring results are intrinsically associated with a person and thereby have far greater potential to generate concern and action, for good or ill.
- The social and political climate in which the new technology of biomonitoring has emerged is itself volatile; contentious and potentially fractious policy debates and litigation surround the field and render it likely that studies will be conducted or interpreted to meet the agendas of specific parties unless great care is taken to establish uniformly agreed on scientific standards against which any study can be transparently judged.

Figure 4-1 presents a schematic diagram of the various considerations in the design of a biomonitoring study addressed in the chapter as well as Chapters 5 and 6 and their relationship to one another. The four stages of any biomonitoring study are study design, study conduct, data analysis, and communication and implementation of results. Each stage incorporates several steps, which follow in chronologic order and are linked in Figure 4-1 by thick arrows. Several disciplines and processes, linked to the main steps by thin arrows, can be engaged in concurrently and are used to inform decisions made for the main steps. For example, biomarker selection and validation usually follow from study hypothesis and population selection, precede participant enrollment and consent, and are informed by statistical considerations, toxicokinetics, ethics, and communication. Study-population selection must take place before study inception. The main steps from population selection through statistical analysis are described in this chapter. Chapter 5 takes up interpretation of results, and Chapter 6 deals with communication of results.

In sum, the purpose of this chapter is to lay out—for the scientific, medical, legal, and policy communities—broad guidelines aimed at guaranteeing that biomonitoring studies will lead efficiently to identification of environmental contaminants that are causing risk or harm while elucidating sufficient information regarding pathways of exposure and health effects to guide their future control and will avoid the creation of widespread anxiety or apathy about contaminants whose potential for personal or societal risk appears not to warrant that reaction.

The discussion will proceed by reviewing the major issues in selection of biomarkers for study, developing the sampling strategy to answer the study questions, and assessing the communication and ethical considerations that must be addressed before the study is conducted. Next, the chapter will review the major considerations regarding the execution of the study, selection of the appropriate matrix (such as, blood or urine), collection of samples, transportation of samples to the laboratory, analysis of the samples, and banking of the specimens, when relevant, for future additional analyses. Finally, we review key considerations in the statistical analysis of the laboratory results.

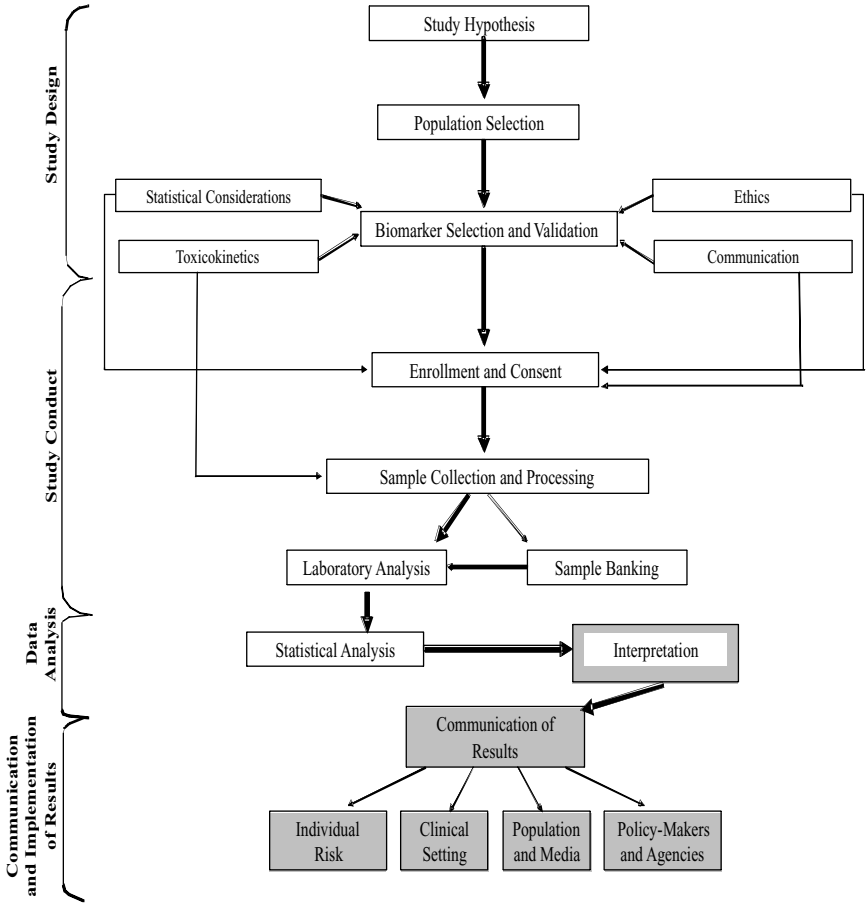

FIGURE 4-1 Stages of a biomonitoring study.

The committee deliberately incorporated discussion of communication and ethical considerations into this chapter not only because these issues present some of the most significant challenges with respect to interpretation and use of the biomonitoring data (key considerations in the committee's charge), but because it was the committee's intent to prompt readers to consider these issues as intrinsic in the design of biomonitoring studies.

STUDY DESIGN

Design of a biomonitoring study incorporates several key components, including consideration of the study hypothesis, the properties of the bio-

markers to be used, the selection of the population to be sampled, and ethical and communication issues. Each of those components will depend on the intended uses of the biomonitoring data.

Relevant Considerations in the Selection of Biomarkers

Several criteria must be considered in selecting a biomarker. The criteria—which include sensitivity, specificity, biologic relevance, and practicality—should be met regardless of the intended use of the biomarker (Metcalf and Orloff 2004; NRC 1991). However, rarely does a biomarker satisfy all the criteria (Metcalf and Orloff 2004). The relative strengths of the criteria for a particular biomarker should guide its applications, as discussed in Chapter 3. In addition to the criteria listed above, information on the kinetics of a biomarker is critical to its use (Bernard 1995).

A description of the criteria for biomarkers follows with illustrations of how they may influence a biomarker's use.

Sensitivity

A biomarker should be capable of measuring a chemical or its metabolites after exposure. It should vary consistently and quantitatively with the extent of exposure (especially at low doses) (Bernard 1995; NRC 1987). However, exposures in community settings are typically lower than exposures in the occupational setting. So, for instance, in measuring chemicals in the workplace, the required limit of detection may be much higher than that needed for assessing environmental exposures in the general population.

Figure 4-2 illustrates the contribution of environmental and occupational exposure to biomarker concentrations and the effect of a method's limit of detection, LOD (or limit of quantification), on potential uses of the biomarker. The example assumes that the biomarker's concentration in a given biologic medium results from endogenous processes and from external exposure to a chemical. If the environmental (or community) exposure is sufficiently large compared with the endogenous contribution, then, given the variability of the latter, the environmental exposure might be reliably assessed, provided that the analytic method has sufficient sensitivity. In the graph, a method with a limit of detection LOD1 would be adequate, but not a method with a sensitivity of LOD2.

If workplace exposure to the chemical is large compared with both endogenous and community exposures, the biomarker could be very useful as a tool for preventing adverse health effects, even with the less sensitive analytic LOD2 method. There might also be cases where the extent of community exposure may overlap with occupational exposure and still

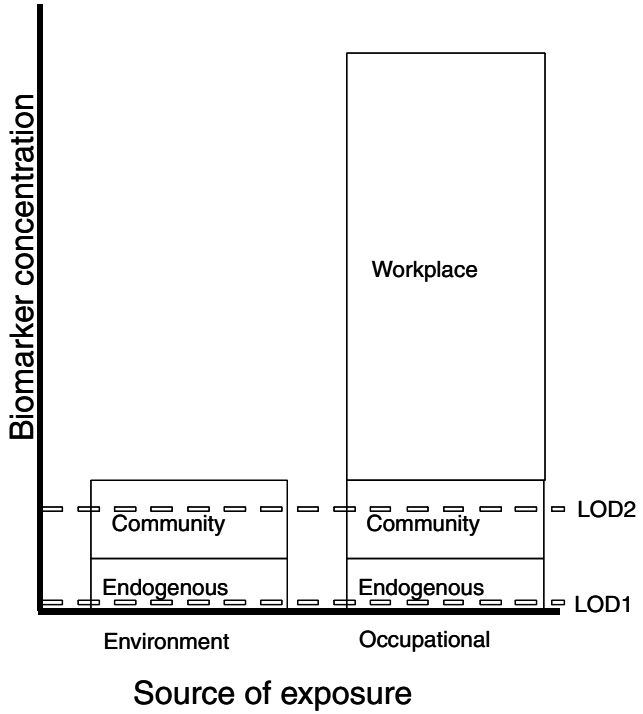

FIGURE 4-2 Contribution of exposures to biomarker concentrations and effect of limit of detection (LOD) on its potential uses.

others where the endogenous contribution to a biomarker concentration exceeds that of community exposure to the parent compound.

Specificity

The biomarker should be specific for the chemical or metabolites of interest; that is, it needs to be an unambiguous marker of exposure. Measurement of the unchanged parent chemical may have greater specificity than that of the metabolite, which may be common to several substances (Bernard and Lauwerys 1986). For example, if the metabolite of the parent chemical is being measured, the result may be equivocal if the same metabolite is produced endogenously or formed after exposure to other compounds. Occupational exposure to high air concentrations of benzene was formerly monitored by testing for its metabolite, phenol, in urine. However, the use of phenol to measure small environmental exposures to benzene is problematic in that many foods contain phenol, and the normal

catabolism of proteins in the body also gives rise to phenol excretion (Metcalf and Orloff 2004).

An example of a nonoccupational exposure is methanol, which is formed endogenously, probably as the result of the activities of intestinal flora or enzymatic processes. It is present in a number of consumer products. Methanol may be present in low concentrations in some foods, juices, and alcoholic beverages. Methanol can also be derived from the intestinal enzymatic hydrolysis of the artificial sweetener aspartame, which results in methanol absorption from the intestine (Butchko et al. 2002). It is estimated that a 355-mL serving of aspartame-sweetened beverages and of various fruit and tomato juices may contribute about 20-100 mg of dietary methanol (Butchko et al. 2002). For comparison purposes, exposure at the current Threshold Limit Value time-weighted average of methanol (262 mg/m^3) would result in a daily dose of about 1,500 mg, assuming an 8-hour inhaled volume of 10 m^3 of air and absorption of 57%.

Biologic Relevance

The biomarker should be relevant to the exposure-disease continuum. However, as discussed in Chapter 3, depending on the information that a particular biomarker provides, it is critical to consider what is known about it with respect to exposure vs health effect. As our scientific knowledge increases, our understanding of where biomarkers lie on the continuum may change (NRC 1987). That is made clear by Schulte and Talaska (1995), who define biologic relevance of markers as the extent to which they represent the underlying biologic event. The authors state that "without demonstration of a direct relationship to exposure and outcome, each biomarker study is actually a test of the biological relevance of the marker and adds to the web of association."

However, biomarkers are being used even when there is little information on exposure or health effects. The classification of biomarkers described in Chapter 3 provides a useful framework for thinking about the characteristics of biomarkers that make them relevant and useful for various applications and provides an important assessment of potential research gaps.

Practicality

Several practical considerations are important in the collection and analysis of biologic samples. A sample should be readily obtainable, storable for a certain period, and capable of being analyzed. (More information on the choice of matrix and logistics of sample collection and processing will be presented later, under "Sample Collection and Processing.") The

cost of analyses is a key consideration in that it often limits the number of participants in community investigations. For instance, analytic costs can be $15-20 for a simple blood analysis or $1,000-2,000 for an analysis of dioxin congeners (Metcalf and Orloff 2004).

In large population-surveillance studies, such as those used by the Centers for Disease Control and Prevention (CDC), biomonitoring is usually conducted on urine and blood samples. However, in research investigations, other matrices—such as breast milk, cord blood, and breath samples—may be used.

The specific biomarker used will also depend on its intended application and the population that is being sampled. For reasons of practicality and study participant convenience, most investigators collect first-morning voids or spot urine samples (Barr et al. 2005a). One recent study in children concluded that measurements of organophosphate metabolites in the first morning void more accurately represented total daily exposure than measurements in spot urine samples collected at other times during the day (Kissel et al. 2005). However, a first morning void specimen might seriously underestimate daily workplace exposure to a rapidly metabolized chemical, whereas one collected at the end of the workday would overestimate 24-hour exposure. Exposures that are episodic over a period of days might be missed entirely with either sampling regimen, but a spot urine sample could be representative of situations involving chronic exposures and intermittent exposures occurring on time scales less than the compound's metabolic half-life (Barr et al. 2005a).

With regard to blood samples, for some analyses, such as dioxins, large samples of blood (70 mL or more) are required, and collecting this volume may eliminate some susceptible subpopulations, such as children and pregnant women (Metcalf and Orloff 2004). CDC's National Center for Environmental Health does not collect blood samples on children less than 6 years old except to analyze lead and cadmium (and in the future mercury), because it is difficult to collect the necessary blood volume (J. Osterloh, CDC, personal commun., July 27, 2005).

Pharmacokinetics

A key consideration regarding the practical aspects of biomarkers is the pharmacokinetics of the chemical. The measure usually referred to is the half-life, which reflects both the affinity of the chemical for the biologic matrix and the efficiency of metabolic or elimination processes. Knowledge of half-life is important for several reasons, including its use in determining sampling time (Bernard 1995). For instance, chemicals with short half-lives (a few days or even a few hours)—including cotinine, phthalates, volatile

organic compounds, and current-generation pesticides—are rapidly eliminated from the body.

For chemicals with short half-lives, the biomonitoring result will reflect only very recent exposures, within the past several hours. As Figure 4-3 shows, the shorter the half-life, the more recent the exposure has to be for it to be detected in a biomonitoring sample. This makes the relative timing of the exposure vs the taking of the biomonitoring sample, a critical determinant of the biomonitoring result. Since the biomarker concentration decreases with time, knowledge of the time lapsed between exposure and sampling is needed to calculate the dose correctly. In practice, it is usually difficult, if not impossible, to tell with any accuracy when exposure occurred. Thus, variability in sampling time (in relation to exposure) introduces huge variability in dose estimates. Additional indexes of past exposures (such as, job classification and information from exposure questionnaires) may need to be collected (Bernard 1995). However, a biomarker with a short half-life can still provide a reliable internal dosimeter if exposures are relatively constant. Cotinine, for example, has a half-life of 15-40 hours in serum, but a single determination provides a good dosimeter of steady-state concentrations in people who have stable smoking habits (Kemmeren et al. 1994).

Biological half-lives of most phthalates are also short, on the order of hours, so that urinary metabolites likely reflect exposures over only the preceding day (Hauser et al. 2004). Nonetheless, monoester metabolites of four phthalates have been detected in greater than 75% of urine samples collected in the 1999-2000 NHANES (Silva et al. 2004) indicating that exposures in the United States are commonplace and frequent. In a study of five phthalate metabolites that were measured in repeat spot urine samples collected over three months from ten men (n = 90 samples), Hauser et al. (2004) concluded that the measurements of metabolite levels in a single spot urine sample were moderately predictive of exposures, with sensitivities and specificities ranging from 0.56 to 0.90 for the various phthalate metabolites for a single urine sample to predict the highest 3-month average. The measurement of the phthalate metabolites in two spot urine samples 1-3 months apart was sufficient to capture within person variability, considering both month-to-month and day-to-day variance (Hauser et al. 2004).

For chemicals with half-lives of months or years—such as dioxins, polychlorinated biphenyls (PCBs), polybrominated biphenyl ethers, and first-generation halogenated insecticides—biomarkers can detect exposures months or even years after they have occurred. Such lipophilic chemicals are usually measured in blood, and the principal exposure source is usually diet. After ingestion, they are readily absorbed into the blood supply; blood concentration then decreases rapidly as the blood supply equilibrates with

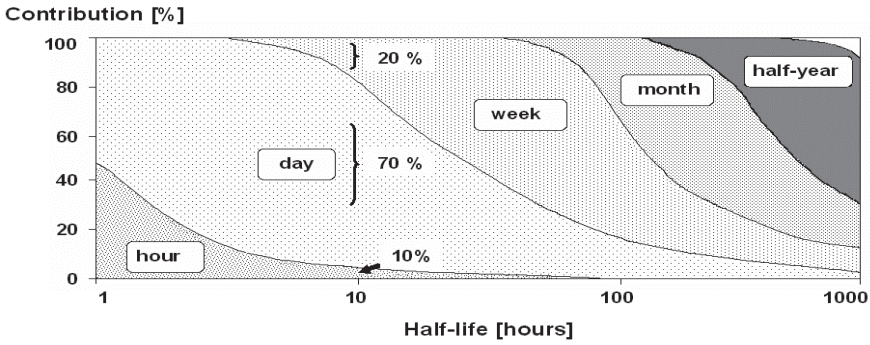

FIGURE 4-3 Effect of half-life on contributions of exposures during the last pre-sampling hour, day, week, month, and half-year to biologic levels of determinants. Half-lives were calculated by a one-compartmental model. For example, if the determinant is eliminated with a half-life of ten hours, the biological level mainly reflects the exposure on the day prior to sampling (contribution of 70%); to a relatively small extent, it reflects the exposure during the previous hour and week (contributions of 10% and 20%, respectively). Source: ACGIH 1995. Reprinted with permission; copyright 1995; American Conference of Governmental Industrial Hygienists.

lipid-rich tissues (Flesch-Janys et al. 1996). After the initial rapid equilibration, the concentration measured in a blood sample is related to body burden and so should not change substantially in the short term.

The importance of the biologic half-life is illustrated with a hypothetical example in Figure 4-4. A biomarker with a short half-life (such as 1 day, in the upper right graph) yields information only about the most recent exposures and does so only if the time of sampling in relation to exposure is known. For a biomarker with a long half-life (such as 1 year, in bottom right graph), the concentration continues to build up over time, so the total exposure duration (and age) of the person is a key factor. In this case, it may be difficult to follow exposure trends in the same people. In geographic population surveys, it may be advantageous to have intermediate half-lives (such as 1 month, in the bottom left graph), in which case a pseudo-steady-state is reached so that the biomarker concentrations reflects continuing average exposure with little influence from sporadic exposure peaks, age, or migration of people to the area under study.

The example given here is representative of many environmental pollutants that are ingested in food. The reasoning can be the same for biomonitoring of ambient air pollutants in the workplace, but the time scales would usually be minutes, hours, or days rather than days, months, or years. In conclusion, the half-life of the chemical needs to be considered in

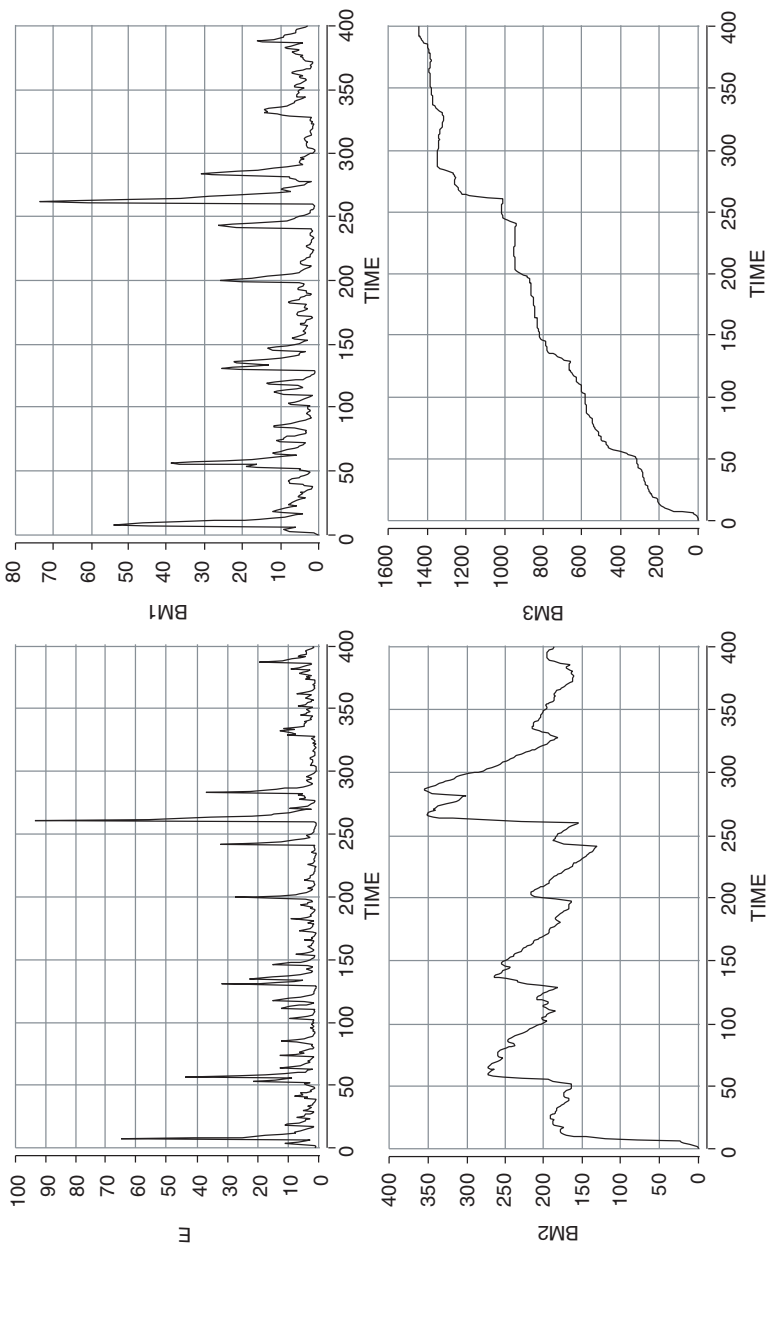

FIGURE 4-4 Influence of biologic half-life relationship between exposure level (E, upper left) and biomarker level (BM). Daily exposure levels were created by Monte Carlo sampling from auto-correlated lognormal distribution. Observation time is 400 days. Biomarker levels were calculated for three half-lives—1 day (upper right), 1 month (lower left), and 1 year (lower right)—with one-compartment pharmacokinetic model.

relation to the time spans of exposure duration, temporal variations in exposure, and sampling.

For the sake of simplicity, simple monophasic pharmacokinetics (one compartment and one half-life) was assumed in the above example and in many other examples in this report. In real life, most chemicals express biphasic or polyphasic pharmacokinetics (several compartments and several half-lives). Squeezing a polyphasic pharmacokinetic behavior into a one-compartment model by assuming a single half-life may lead to negligible errors for some chemicals and serious misinterpretation of biomarker concentrations for others. The same can be said about nonlinear processes, such as metabolic induction, inhibition, and saturation. A good way to check the accuracy of a simple pharmacokinetic model is to verify its performance by comparing with a physiologically based pharmacokinetic (PBPK) model that may encompass the mentioned factors.

In conclusion, great effort should be made to develop a human pharmacokinetic, preferably PBPK, model early in the study design. The likely influence of, for example, model simplification (such as assuming a single half-life), metabolic saturation (see, e.g., Liira et al. 1990), and sampling time can then be addressed before investment of vast resources in sampling and analyses. By using statistical tools (Monte Carlo simulation and population models) in the model, one can examine additional features, including variability in exposure pattern (e.g., Nihlén and Johanson 1999) and intraindividual and interindividual variability in pharmacokinetic determinants, such as workload (e.g. Droz and Fernandez 1977), body build, and metabolic genotype (e.g., Jonsson and Johanson 2001).

Sampling of Populations

In exploratory investigations, studies of occupational groups, and clinical applications, the choice of subjects on whom biomonitoring should be done is generally straightforward. However, for most other applications (see Box 3-1), values of exogenous chemicals in blood or urine cannot practically be obtained from every member of the group of interest. Instead, researchers or public-health authorities have no choice but to obtain specimens on a *sample* of the population, from which statistical inferences will later be drawn regarding the (generally much larger) group as a whole. To be successful, the strategy, similar in concept to taking a poll before an election, must be performed in a scientifically valid and efficient way. For one thing, if results are to be extended across all age groups and both sexes, adequate numbers of males and females of all ages must be included in the sample. If there is reason to suspect the importance of some special factor as a determinant of levels, such as proximity to a source or dietary preference, people with various levels of such "risk factors" should be included.

But whether the purpose of a study is exposure surveillance or exploring cause-effect relations between an environmental chemical and ill health, "inclusiveness" alone is not sufficient to ensure that results can be usefully extrapolated to the larger group. The people chosen must also be generally representative of others in their age, sex, risk class, or any other characteristic considered a priori to be important. Polling organizations go to considerable lengths to achieve just that; the three waves of biomonitoring performed by CDC in the National Health and Nutrition Examination Survey (NHANES) are a model effort from this perspective. For various reasons, some scientifically justifiable and some not, some researchers choose samples of convenience. Convenience sampling tends to be the norm rather than the exception. For example, it is far more convenient to obtain the requested numbers of people in a small geographic area or to take specimens from people who appear at a clinic or hospital for unrelated reasons. Such groups may have the right mix of age, sex, and other characteristics specified, but they may be just convenient, and not representative of any larger group. Likewise, there have been numerous reports of groups assembled because they responded to solicitations to participate in studies of environmental effects. Although it may be possible to draw some insights from such groups of self-selected volunteers, they cannot be presumed to be representative of a population of interest, nor can any valid comparisons with unsampled members of the population be made.

Selection bias is the Achilles heel of such samples. Therefore when researchers use convenience samples for assessing population characteristics such as prevalence, incidence, or causal relationships, they must justify the validity of the sample.

At a minimum, when such convenience samples are reported, the strategy used for recruitment and selection must be made completely transparent and explicit so that scientists can assess the distortions or biases that may result from analyzing measurements in such groups as though they were true population samples. The committee recommends that if convenience samples are chosen, then funders, reviewers, and editors of peer-reviewed journals must insist on complete characterization of how each sample was chosen so that misinterpretation—intentional or not—is less likely.

Even if those principles are rigorously adhered to, there remains in every situation an important degree of uncertainty because of random variation—who was sampled and who was not—so all results will ultimately need be expressed with respect to that uncertainty (see Statistical Analysis below). In general, the smaller the group sampled and the larger the variation in values because of interindividual differences and laboratory variation, the more uncertain the results will be. Two strategies should be used by researchers in assessing precision. If a single population is of interest (intrinsic inference),

means or other statistics, such as medians or interquartile ranges, can be estimated with a required degree of precision which determines sampling effort. If the comparison of two populations is of interest (comparative inference), the power of the proposed sampling strategy should be assessed in order to detect meaningful differences between the two populations. This will allow the study subjects, ethical review panels, and funding agencies to assess the likelihood that the study will answer the intended questions. The questions surrounding biomarkers will involve comparisons of populations; therefore the emphasis should be on statistical power.

The committee recommends that biomarker researchers, public or private, should adhere to appropriate statistical principles when sampling populations for biomonitoring. Editors of peer-reviewed journals as well as agency administrators and reviewers should insist on explicit attention to such information to minimize the possibility of incorrect inferences—even more while the biomonitoring field remains exploratory and public understanding remains incomplete.

Covariation–Socioeconomic Status, Race, and Ethnicity

As mentioned previously, one of the central dilemmas in the development of biomonitoring strategies is the lack of information about the factors that may determine which people have higher or lower concentrations of widely disseminated chemicals in their bodies. Little is known about how some people might be exposed to many of them, let alone how they are absorbed, metabolized, or excreted or what other genetic or environmental factors may modulate exposure. It is essential, therefore, that in all biomonitoring studies as much information as possible be obtained about each study subject, including not only the obvious factors—such as age, sex, and geographic location—but other relevant characteristics such as personal habits, lifestyle, and living circumstances whenever feasible. When biomonitoring results are presented in relation to each of those characteristics, valuable insights may be gleaned regarding sources of exposure and factors that modify exposure.

Covariates of particular importance are factors related to socioeconomic status (SES) and related demographic factors, including race and ethnicity. There are several reasons for collecting that information rigorously and displaying results of biomonitoring studies in a way that readily elucidates the relationship between biomarker concentrations and SES characteristics. Because income (or wealth), occupation (or social standing), and educational attainment may be closely associated with exposure, "stratification" of the data could provide clues about particular aspects of life that are most closely associated with magnitude of exposure. Such information may be important for understanding of the social distribution of whatever

potential health risk that exposure to the measured chemical may confer. There is widespread belief that environmental risks are not evenly shared by the population—that poorer people and ethnic minorities are subject to a disproportionate share of the potential harm (IOM 1999). Whether environmental injustice is typical of many chemicals or is limited to a few serious toxic chemicals, such as, lead, remains to be established. If biomonitoring data were consistently presented in association with SES data, the extent of such "maldistribution" might be clarified. Because of the sampling strategy, the first three waves of the CDC NHANES had, by design, sufficient power to provide all results in relation to race but not in relation to SES factors more generally.

For all those social and lifestyle-related factors, there is an even more important reason for rigorous attention to covariates during study design. The goal of biomonitoring is ultimately to identify the health effects of environmental factors so that risk can be controlled. Therefore, it is crucial that the relationship between health and environment not be "confounded" by other factors associated with both high biomarker concentrations and adverse health characteristics. Any factor associated with both a higher biomarker concentration and a disease of interest is a potential confounder. It is well established that the risk of many chronic diseases, including most heart and lung diseases and cancers, correlates inversely with education, income, and social position (Marmot et al. 1991); and it is likely that at least some biomarkers will, like lead, correlate directly with such factors as low standards of housing, job type, and diet. In tandem, those two relationships render it likely that cause-effect relationships may be erroneously inferred between some biomarkers and adverse health effects and that the wrong control measures will be chosen. Alternatively, it may turn out that one or more of the measured chemicals may actually *explain* an SES-health link or part of a link. But this possibility cannot be meaningfully evaluated without detailed knowledge of the relevant characteristics for each subject in biomonitoring or epidemiologic studies that use biomarkers.

The committee recommends that investigators, including CDC, that conduct surveys of biomarkers in the population should routinely collect detailed information about SES, lifestyle, and other cofactors on each subject and routinely present results organized so as to address the question of whether biomarker concentrations vary as a function of each. Epidemiologic analyses of biomarkers in relation to health should routinely include appropriate adjustments for such covariates.

Intra-individual and Interindividual Variability

In addition to SES, race, and ethnicity, biologic variation between and within people must be considered in sampling populations because at a

given exposure dose or dose rate, the true concentration (assuming no sampling or measurement error) may vary considerably between people owing to differences in pharmacokinetics (absorption, distribution, biotransformation, and excretion of a chemical). Most pharmacokinetic factors may also change within a person, causing variation within people. For example, the absorbed amount of inhaled pollutants varies with pulmonary ventilation, which in turn depends on body size and level of physical exercise. Fat-soluble chemicals tend to be redistributed to and accumulated in adipose tissues. The distribution of such substances depends on the amount of and blood flow to adipose tissue in the body. Body build and obesity depend on genetic factors, dietary habits, and exercise, all of which may vary between ethnic and socioeconomic groups and geographic regions. Accumulation in adipose tissue (or any other tissue) tends to lower a chemical's concentration in blood and urine during exposure and increase the concentration after exposure, causing additional variation.

The rate of biotransformation of a chemical depends on the amount and efficiency of the pertinent biotransformation enzymes. Enzyme activity is partly genetically determined but may also vary between and within people because of enzyme induction caused by previous exposure to the same or related chemicals. Variation in enzyme activity may also be caused by enzyme inhibition due to concurrent exposures.

There is increasing concern for infants and children as susceptible subpopulations (Daston et al. 2004), in that differences in physiology and behavior can lead to higher exposures in young children than in adults. Young children eat, drink, and breathe more air per unit body weight than adults (Daston et al. 2004, NRC 1993), but children also differ from adults with respect to ratios of fat, muscle, and water; higher metabolic rates per unit of body weight; and immaturities in enzymatic systems (Ginsberg et al. 2004). Those differences can increase or decrease risk, depending on the mechanisms of action (Ginsberg et al. 2004).

An important aspect to consider in biomarker population variability is polymorphisms in the biotransformation enzymes. A polymorphism is typically defined as a genetic variant that appears in at least 1% of a population (Nebert 2000). Those genetic variants may in some cases produce enzymes that have higher or lower activity. Most of the more than five dozen human pharmacogenetic differences described represent alterations in the drug-metabolizing enzyme genes. Pharmacogenetic differences in metabolism can be striking, often 10- to more than 40-fold (Nebert 2000). One or both alleles[1] may also be lacking. For example, in the case of glutathione transferase T1 (GST T1), people with two normal alleles for GST T1 will have

[1]An allele is one of the variant forms of a gene at a particular locus, or location, on a chromosome.

high enzyme activity, those with one normal and one lacking allele will have intermediate activity, and those with two absent alleles will have zero activity of GST T1 (Lof et al. 2000; Warholm et al. 1994). The frequencies of polymorphisms vary between ethnic groups and between different parts of the world (see for example, Kaneko et al. 1999; Mizutani 2003). As a consequence, the relationship between magnitude of exposure and biomarker concentration will vary. At present, there are limited data available on the relations between genotype and population variability in biotransformation rate of environmental toxicants. However, with the ongoing development of high-throughput techniques and pharmacogenomics, the knowledge in this field is likely to grow rapidly.

The influence of pharmacokinetic factors—such as physical exercise, body build, diet, and polymorphisms—on interindividual and intraindividual variability in biomarker concentration depends on the physicochemical characteristics of the chemicals. The relationships are often difficult to describe with simple, general rules. It may be advantageous to use PBPK models to understand their influence. (These are described in Chapter 5 and Appendix B.)

Ethical Aspects of Biomonitoring

Despite the extensive experience with biomedical ethics, the infrastructure of institutional review boards (IRBs), and the equivalent for protection of human subjects (Schulte et al. 1997; but see Soskolne 1997), it is essential to address questions of ethics that may be particular to the design of biomonitoring studies. In this section, the committee considers some practical and research issues in biomonitoring ethics but makes no pretense that the list is exhaustive. Ethical issues can stop specific studies, and the field in general, dead in their tracks. Therefore, it is incumbent on investigators, policy-makers, and others to consider these issues carefully.

Practical Issues

First, IRBs' scope—and thus potential protection for human subjects in biomonitoring studies—is not universal. Fairchild and Bayer (2004) noted with regard to the United States the "necessity of ethical review of public health surveillance activities at both state and federal levels, whether such activities fall neatly under the classification of research or practice or exist in a gray borderland." Similar gray or black areas exist for many agencies that lack any IRB infrastructure or even awareness that it might be valuable, perhaps for some corporate and activist-group operations, and for for-profit biomonitoring firms soliciting business from individuals. The committee would encourage all entities that sponsor or conduct biomoni-

toring studies to either establish an in-house IRB or equivalent, or arrange with an external organization to provide that service, so that any gaps in formal ethical assessment and informed consent are filled.

Second, IRBs can become overzealous in insisting that biomonitoring data be anonymous rendering biomarker results untraceable to an individual and his or her personal characteristics. The only value in biomonitoring efforts in the long run is the ability to assess human health effects, and this makes it necessary to link sample results back to human health and risk-factor information. Unless a sample is taken solely to establish ranges in a population, no biomonitoring researcher should render samples useless by severing links between them and current or future health data. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC 2005) endorsed the notion that anonymous data are "problematic" if they concern a treatable or preventable health impairment, but the committee considers that the problem is larger and could present a major barrier to progress in biomonitoring. IRBs and researchers have enough experience with methods for keeping personal data confidential—for example, the pharmaceutical industry's use of double coding, recommended by ECETOC (2005)—for this allowance for biomonitoring data to be neither unethical nor impractical even without the support offered by legislation in some countries (such as the Health Insurance Portability and Accountability Act in the United States, HIPAA).

Third, a generic warning about potential consequences of group results and the significance of personal measurements should be a default provision in informed-consent forms for biomonitoring studies in general. For example, if a biomonitoring study reveals that the internal dose of a population living near a polluting plant has reached intolerable levels, a policy decision might be made to close the plant or move neighboring residents. It is crucial that health, economic, regulatory, and other ramifications for all potential constituencies be considered by both study designers and study subjects before the study begins. In practice, that may be difficult, particularly when results of a "research" study never intended to provide "policy" advice are used by policy-makers—with or without the concurrence of researchers—to decide such major issues. However, difficulty is not a proper reason for limiting ethical obligations. A similar situation arises when an individual learns of an elevated concentration of the chemical in the body, but the relationship to health effects is not known. The committee considers that it is better for the individual to possess this information than not, as sampling in the individual provides very valuable information for population-based exposure studies that can advance public-health knowledge and ultimately benefit the individual.

Fourth, despite debates over what to tell study subjects (e.g., Schulte et al. 1997; Veach et al. 2001; Grill and Hansson 2005; Kass 2005), the

committee considers that subjects should be told (or offered the chance to be told) whatever researchers know (or do not know—see uncertainty discussion in Chapter 6) about the topic. If the meaning of results for potential health effects is clear, but potential options are not obvious (for example, because biomarkers are from groups V-VII, for which data on external exposure pathways or sources may not be available—see Chapter 3), the disclosure method used for some kinds of genetic testing should be considered. For Huntington's disease, for example, genetic testing can with high confidence confirm whether an individual will get this fatal disease, but there is no known treatment or cure. As a result, people with a family history of the disease vary widely in whether they choose to get the test (for instance, "I want to know so I can be prepared" vs "What good does it do to know if nothing can be done?"). Giving biomonitoring research subjects the same option is desirable. In other situations (such as for group III or IV substances), the health implications of biomarker concentrations for an individual may be unclear, but possible actions are obvious, such as when chemical exposure can be easily reduced by individuals' actions. In this case, the relative contribution of different sources to exposure or of different actions to exposure reduction should be explained. If there is some uncertainty about the information, it could be accompanied by a warning that action may be wasteful or counterproductive *from the perspective of the individual subject*. Therefore, understanding the subjects' mental models about biomonitoring (see Chapter 6) is an important aspect to obtaining true informed consent. Empirical research on this topic will be necessary to improve the conduct of biomonitoring studies from the ethical perspective.

Fifth, studies proposing to sample human tissues must carefully lay out tradeoffs—without exaggerating either benefits or risks implied by the sampling, the body tissue, or sources of biomarker chemicals—in both consent forms and reports of final results. The challenge of how to search for and convey potential dangers without ignoring or downplaying potential benefits of risk-bearing activities is exemplified by efforts to use breast milk for biomonitoring. Concerns over how to communicate risks vs benefits of breastfeeding in 2005 helped to block recent California legislation on biomonitoring. Breastfeeding offers great benefits of nutrition and immunity to infants but also might transfer a relatively high concentration of chemicals to those infants at a vulnerable point in their development. Given the undeniable benefits of breast-feeding and the fact that a substantial portion of babies in the United States do not receive them now, poorly designed and publicized breast-milk biomonitoring studies could yield more harm than good. Yet breast-milk studies should be conducted, because little can be done to keep chemicals out of breast milk without such information (Risk Policy Report 2001), and a single measurement provides the chemical-exposure profile for the mother and the exposure dose for the fetus. This

issue is more challenging than warning people about mercury or PCB exposures from eating specific fish species without discouraging their obtaining the benefits of fish oils. There are benefit-equivalent but lower-risk alternatives for fish that are not available for breast milk. However, the mercury analogy underscores the importance of identifying and conveying guidance to these mothers on potential sources of chemicals in their breast milk so that (as with fish consumers) choices can be made about how to reduce exposures.

Sixth, committee deliberations raised two ethical issues whose occurrence, seriousness, and resolution were uncertain but that deserve tracking and possible future practical or research action. Only open discussion between scientists and ethicists can promote consensus on the issues, and the committee would be remiss if it did not encourage that discussion by mentioning them here. One question is how to report and respond to those with higher exposure levels when health implications are unknown. Secondly, is it ever appropriate to "require" biomonitoring of higher risk populations such as those occupationally exposed?

Research Needs

There are three high-priority research needs for biomonitoring ethics. The first is for research that develops, evaluates, and disseminates methods for ethically and practically informing subjects (during both recruitment and debriefing) in studies that use high-output, high-throughput technologies. For studies that develop a biomarker, researchers should provide as much information as possible on the biomarker and its parent chemical. Currently, participants in a public-health study measuring hundreds of biomarkers might give "informed consent" only with respect to the general objective of the study (although some biomarkers might not be fully validated). Detailed discussion of each biomarker is prohibitive. However, failing to provide more detailed information about all biomarkers to be measured, no matter how many chemicals are involved in the study, raises ethical questions that merit consideration.

The second research recommendation is for the development of new methods for obtaining blanket consent for future uses of biomonitoring data that are ethical and practical. Concern that blanket consent (for instance, for future testing of tissue samples with genomic or metabonomic assays that are not available at the time of study recruitment) would be open to abuse has increased the difficulty of obtaining IRB approval. The committee is sympathetic to such concerns but is aware of the ethical (and practical) problems posed by the undue replication of tissue sampling that this implicit ban forces as each new sample application is imagined. In pursuing this research, it would be prudent to assess "mental models" of

various constituencies (see Chapter 6) about blanket consent in the context of biomonitoring. In addition to understanding the beliefs and concerns of IRBs about blanket consent and how they might overlap with those about anonymizing data (see previous section), this step could inform development of blanket-consent approaches that are as widely understood and acceptable as possible.

The third research recommendation is to conduct empirical research on the mental models of the general population about biomonitoring, as also recommended in Chapter 6 for the purpose of communication results, interpretations, and uses. One ethical reason for this research would be to understand the population's concerns about participating in biomonitoring studies, since participation rates in some countries have been depressed to the extent that the apparent need for incentives could compromise ethics if incentives are too high. Research on biomonitoring concerns can address these issues, as well as help ensure that better informed consent will be obtained from biomonitoring study participants.

Two issues have been identified in addition to those three high-priority research needs. Better understanding is required on how the framing of research, through the language used, can affect subject recruitment, policy implications of study results, and other applications (Schulte and Sweeney 1995). For example, inhalation exposure to a solvent in an occupational setting can often be assessed by roughly equivalent measures for the purpose of controlling exposure: measuring its atmospheric concentration or a urinary metabolite. But the fact that a urinary metabolite is a "biologic" substance sometimes creates far different legal and ethical obligations from its equivalent "chemical" counterpart. A biomarker concentration considerably below guideline levels might have to be declared to public-health authorities, whereas there is no such obligation regarding air concentrations even just below legal limits. In another example of language's power to bias responses, some people may refuse to participate in a study because of the methods and terms used—for example, urine connotes testing for illegal drugs, "genetic" connotes a revelation of health problems to insurers—thus potentially affecting a study's outcome or even whether it is feasible. Research that directly examines the extant framings (intended and unintended) and alternative framings of biomonitoring by researchers, policy-makers, stakeholders, and the mass media will help to advance the field and encourage all parties to consider possibilities that might otherwise not be apparent in biomonitoring ethics and communications.

Finally, it is important that biomonitoring projects document (in widely available reports or in the communications database discussed in Chapter 6) the ethical challenges and solutions (and evaluations of those solutions) that they face. Biomonitoring sponsors could aid in this task by requiring that project proposals address how they will document the issues. The data can

then become grist for research that identifies potential new ethical challenges and procedures. Just as all future uses of biomonitoring tissue samples cannot be envisaged, neither can all ethical issues related to biomonitoring. Ethics documentation provides a resource that may be productively mined for further illumination of this important but all-too-neglected field.

Communication in Biomonitoring Design

Communication is usually seen as a late stage in environmental management: a biomonitoring study, risk assessment, or project or policy decision has been produced, and results must be conveyed to decision-makers and observers. (This is covered in Chapter 6.) Before then, scientific research and public-health investigations focus on "doing the science right" (Stern and Fineberg 1996). Yet early incorporation of communication issues into study design can greatly enhance biomonitoring's value for every biomarker group (Table 3-1). While study purpose and design can certainly influence the content and means of communicating study results, anticipation of communication issues can—and often should—influence study purpose and design. It is for this reason that communication themes discussed below, including constituency assessment, consideration of partnerships, and planning for evaluation, are crucial to the design of a biomonitoring study, as they cannot be easily or effectively incorporated at the end of the study. Therefore the committee recommends that *every* biomonitoring project explicitly include communication issues in project design.

Two issues critical for designing biomonitoring studies are early assessment of constituency[2] views and planning for evaluation of communication effectiveness.

Early Constituency Assessment

Careful consideration of project goals early in the design can help to identify the nature and scope of likely communication goals and problems and thus begin to identify solutions (Pflugh et al. 1994; see Schulte 2005, on biomonitoring specifically). Project goals and communication goals are not identical (Pflugh et al. 1994), and early thinking through of how project and communication goals might support or conflict with each other can improve the eventual success of both. Project and communication goals are

[2]Some people might prefer the term *audience(s)* for those considered in biomonitoring-project design, and those targeted for messages about biomonitoring results (Chapter 6). But *audience* implies passive receipt of information, which is rare and often undesirable in communication. "Constituents" vary widely in the type and quantity of their activity, including being passive audiences, but this term more accurately conveys the appropriate tone.

intimately entwined with the constituencies that will be served by or interested in study results; constituencies and goals mutually determine each other, rather than having a simple one-way link. The constituencies include, at a minimum, study subjects, scientific peers, sponsors, stakeholders, policy-makers (European Commission 2004), the supporting community and larger publics, and the mass media, although these distinctions are somewhat artificial. The intended constituencies (those which project managers tend to plan for) need not include all desirable or actual recipients of project communication, so potential "unintended" constituencies should be planned for as well (with the aim of turning them into intended ones).

Assessment of constituencies entails, at a minimum, identifying their beliefs, attitudes, relevant values, behaviors and behavioral intentions, concerns and questions. Biomonitoring designers can use this information to determine whether and how project design could answer potential constituencies' questions and concerns, and revise the design to improve its ability to meet those needs. That will make their studies more robust in the face of criticisms of poor design or irrelevance, focus disputes on interpretation of data rather than on missing data, and aid the development of appropriate informed-consent procedures and content (Kass 2005). If detailed enough, it can yield the foundation for specific, effective messages about study results (see the "mental models" discussion in Chapter 6). Guides for understanding audience concerns and the communication context (also see Chapter 6) include both overviews of communication planning (Pflugh et al. 1994) and specific assessment methods, such as methods that help to grasp social and cultural aspects of community-based environmental protection (EPA 2002). A given biomonitoring project need not address every possible question of every possible audience, nor will all biomonitoring projects evoke identical interest or questions. However, most biomonitoring research will have eventual applications; researchers who think they will not need to communicate and thus ignore constituency assessment are likely to be unpleasantly surprised.

Practical Issues

First, biomonitoring funders should require communication planning in any application for funding. It is hoped that investigators would spontaneously recognize the value of communication planning and constituency assessment, but sponsor requirements for proposal and study content would clearly signal their importance.

Second, the biomonitoring communication database (see Chapter 6) should include results of studies' experiences: biomonitoring reveals the questions, concerns, beliefs, and attitudes of various constituencies for biomonitoring data, and each practitioner need not reinvent this knowledge

anew. There is likely to be enough overlap in these issues—and how to address them in project design—across projects to make such a database invaluable for later funders and researchers. Relevant data would include the constituency questions considered, the sources of the questions (such as, direct interviews with constituency members on researcher assumptions), and their effects (if any) on project design.

Third, the often tense political and social context in which biomonitoring studies are conducted (see Chapter 4 introduction) suggests that some such studies could benefit from incorporating joint decision-making. This partnership with study subjects or stakeholders in project design is one example of analytic-deliberative processes for environmental decision-making (Stern and Fineberg 1996). The Community-Based Environmental Protection program of the Environmental Protection Agency sponsors one kind of such project-design partnerships; "the community" (or a community association) is not the only or best candidate for all biomonitoring studies, and the "partnership" can vary widely in how much control the nonresearcher partners have. These processes recognize that effective identification of values and application of science pertinent to the values are both essential to good decisions and bring scientists, officials, stakeholders, and citizens together to pursue these goals. Partnerships in policy decision-making are more common, but partnerships in defining research agendas and designs can heighten the breadth and quality of research, build confidence in the research process, and make the results more credible and more likely to be used (e.g., Stern and Fineberg 1996; Stinson and Ehrmann 1998; Ehrmann and Stinson 1999; Lasker and Weiss 2003; Adler 2002; Andrews 2002; Beecher et al. 2005). Among the largest challenges for either implementation or success of analytic-deliberative processes are erroneous beliefs "that analysis = *science* and deliberation = *participation*" and "that we analyze *only* facts but deliberate *only* about values" (Webler 1998; emphasis in original). Other issues that deserve early consideration include large power and expertise imbalances among the potential partners (for example, are study sponsors and partners willing and able to set up a process that minimizes the imbalances?) and whether some benefits of "joint fact-finding" might be produced largely by ensuring that constituency questions are answered by study design (see above). Some constituencies might be represented indirectly by other partners (for example, unions might stand in for workers in occupational studies) but only when study constituencies have interests that can be adequately represented.

Research Recommendations

First, research should be conducted on the best ways to link constituency assessment, project design, and constituency satisfaction and other

evaluation criteria (see next section). Whether it consists of independent empirical studies or is based on analysis of biomonitoring communication database contents, this research would allow a step back from the ad hoc response of individual biomonitoring projects to examine the larger picture. For example, some quick, low-resource assessment methods may be quite useful, whereas others could be misleading about constituency views compared with more intensive methods; some project designs could reliably produce successful outcomes, whereas others might work not at all or only in unique situations. It would be too much to assume that individual investigators could garner that information themselves.

Second, although there is some work on design of analytic-deliberative processes, it is recognized that much more research is needed to understand how to improve their functioning, particularly as the scientific proportion of issue analysis—as in biomonitoring studies—increases (Stern and Fineberg 1996). As noted above, joint fact-finding and other efforts at partnerships in designing scientific studies are less understood than policy-focused analytic-deliberative processes. The committee considers that structuring research projects around such processes applied specifically to biomonitoring issues would be valuable. Research projects around nonbiomonitoring partnerships are likely to be few, with unknown generalizability to biomonitoring, so it would be prudent for biomonitoring sponsors and investigators to pursue this research themselves rather than wait for enlightenment from other fields.

Designing for Communication Evaluation

A second main reason to consider communication in project design is that this is the time to plan for evaluation of communication. There is inevitable interaction between communication goals and evaluations. One needs to know the goals to decide how to measure success or failure in achieving them; if achievement of the goals cannot be validly or reliably measured, goals need to be reframed or revised, because this problem implies that goals have not been fully thought out. Thus, planning for evaluation during or after project implementation is likely to be too late to be useful. An early start also enhances the likelihood that midcourse evaluations can feed into regular reassessments of goals (and possible changes to them), just as goal revision during a project feeds into changes to communication practice and evaluation (Pflugh et al. 1994).

Ultimately, success will be defined by a particular study's goals and thus vary from one study to another. Table 4-1 outlines two approaches for determining and measuring criteria of success adaptable to specific projects: a goal-based approach proposed by Weinstein and Sandman (1993; also see Rohrmann 1992) and a process-based approach focusing more on whether

TABLE 4-1 Goal-Based and Process-Based Criteria for Evaluating Communication

Goal-Based[a]	Process-Based[b]
Comprehension: Message content is understood	Exposure: Message received by audience
Agreement: Interpretation or recommendation in message gains assent	Attention: Message read or heard
Dose-response consistency: Greater risk perception or readiness for action among those who face a higher dose of a hazard	Comprehension: Message content is understood
Hazard-response consistency: Greater risk perception or readiness for action for a higher-risk hazard than for a lower-risk hazard	Confirmation (optional): Complementary information sought from other sources
Uniformity: Similar responses among those facing the same level of risk	Acceptance: Interpretation or recommendation in message gains assent
Audience evaluation: Message's perceived utility, clarity, credibility, helpfulness, accuracy, and so on	Retention: Message content memorized so that it can be retrieved when needed
Types of communication failures: Whether types that occur are more acceptable, given communication goals	Realization: Audience action complies with the message

[a]Adapted from Weinstein and Sandman 1993.
[b]Adapted from Rohrmann 2000, Figure 2.

intermediary steps to comprehension, agreement, and so on are being met (Rohrmann 2000; also see Rohrmann 1992), although these methods often also include goal-based criteria. Further details on these approaches can be obtained from the cited references; Balch and Sutton (1995) also offer suggestions for providing government agencies useful communication evaluations.

Practical Issues

Quality assurance and quality control of biomarker data get far more attention than whether biomonitoring communication goals are achieved and why (Balch and Sutton 1995), despite the importance of both issues. The committee suggests practical ways to improve biomonitoring evaluation below.

First, the benefits of incorporating evaluation planning into project design are more likely if it is explicitly funded as a separate task. Funders should require discussion of communication evaluation in proposals for funding; researchers should explicitly remind sponsors that these are important tasks by including them in proposals even when this is unsolicited. If neither group explicitly includes evaluation tasks in the funding application process, the inadequate status quo will endure (Balch and Sutton 1995).

Second, project designers should consider defining communication success more broadly than by criteria of the study's manager or sponsor or solely with goal-based and process-based "theoretical" criteria. Santos and Chess (2003) showed in evaluating citizen advisory boards that such participants as citizens, officials of different agencies, and activists had criteria for success differing from each other and from those derived from theory. The authors concluded that "using both theoretical and participant-based criteria for evaluation can provide more comprehensive feedback than either method alone" although they noted a need for evidence that mixing these criteria "enhances the legitimacy of the effort and increases use of the evaluation."

Third, the committee recommends that biomonitoring sponsors and researchers consider development of a standard set of criteria and measures to be applied as a default (in addition to study-specific criteria and measures) so as to compare the relative effectiveness of different communication approaches (Santos and Chess 2003).

Fourth, the biomonitoring communication database (Chapter 6) should include study-specific communication methods, evaluation planning, and evaluation results. Little health or risk communication research is currently relevant to biomonitoring (Chapter 6), and this condition is likely to endure if it is shaped solely by investigator-driven communication research. The large and useful literature on evaluation methods and issues (e.g., Comfort 1985; Fisher et al. 1991; Rohrmann 1992; Tinker 1994) does not identify problems and solutions peculiar to biomonitoring. Knowing messages and methods of communication that work, and why, would be invaluable to projects with similar communication goals or biomonitoring data (e.g., see Schulte et al. 1997 on evaluating notifications of individual results).

Research Recommendation

The biomonitoring communication database (Chapter 6) should be used to identify "good" evaluation criteria and feed into development of the "standard" default criteria and measures recommended above. For example, research could contrast goal- vs process-based evaluation criteria, or theory-, investigator-, and constituent-derived criteria, in terms of their ease of elicitation or use or utility in reliably predicting successful commu-

nication. In addition, evaluation research might identify kinds of study goals or designs that are less successful than others, motivating further research on how they might be improved or whether these goals or designs should be modified or abandoned.

Incorporating communication into project planning and design is not difficult, futile, or irrelevant to biomonitoring but is an essential element. Careful attention to effective communication at the beginning of a biomonitoring study will pay off with much easier communication at the end and may even make the technical side of the project more effective.

STUDY CONDUCT

Execution of the study consists of collecting the biologic samples (including considerations regarding sampling time and quality assurance, depending on the matrix—such as blood or urine—used), transporting them from the field to the laboratory, and processing them in the laboratory. If samples are to be saved for future analyses, biobanking may be a consideration.

Sample Collection and Processing

Choice of Specimen

Historically, adipose tissue has been considered the most appropriate matrix for biomonitoring focused on persistent chemicals that bioaccumulate in fatty tissues (see Chapter 2 for more details). In the last 15-20 years, blood and urine have been used more commonly.

The 1991 National Research Council report *Monitoring Human Tissues for Toxic Substances* recommended that any new program to assay chemical concentrations in tissues of the U.S. population be based primarily on analysis of blood. The use of blood permits sampling of a wider sector of the population, better comparison of exposed populations with national averages, repeat sampling of persons who have high tissue concentrations, and opportunities to follow chemical clearance with time. The 1991 report also advised analysis of adipose tissue (especially for persistent pesticides) that would provide continuity with previous studies and confirmation that a survey based on blood also detects important tissue residues of persistent chemicals (NRC 1991).

It is not feasible to study a wide array of tissues in a general population sample, so it is important to identify tissues that most accurately account for the body burden of most of the chemicals of concern. Figure 4-5 shows the main routes of exposure and the matrices available for analysis of biomarkers based on the metabolism and pattern of bioaccumulation and

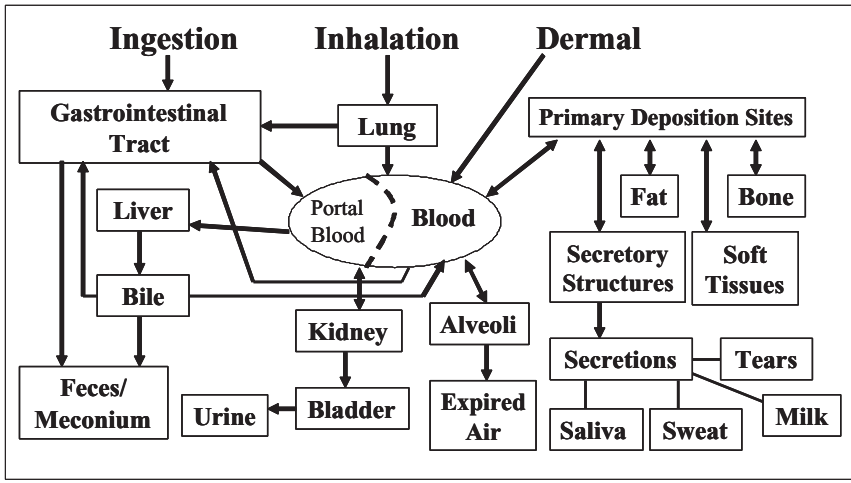

FIGURE 4-5 Pharmacokinetics of environmental chemicals in body and what matrices are available for analyses. Source: Needham et al. 2005.

excretion (that is, feces or meconium, urine, expired air, saliva, sweat, and milk). The choice of matrix for specific biomonitoring depends on the chemical of interest, its persistence, and its deposition.

Not all matrices are readily available for large population studies and for all age groups (Table 4-2). For example, breast milk can be collected only for several days or months and only from lactating women. Cord blood and meconium, which both reflect intrauterine fetal exposure, can be collected immediately after or shortly after delivery.

Matrix choice is also informed by the invasiveness of collection and whether it is appropriate at a given life stage. Urine is one of the least invasive matrices to collect, but its amount varies widely, from several milliliters in very young infants (collected with specially designed diapers) to several dozen milliliters in 2- to 4-year-old children who are already toilet-trained and can use disposable collection units. Finally, in older children and adults, the amount of urine is no longer a limiting factor, and the main focus in consideration of study design shifts to the timing of collection. For example, a morning void may be needed to acquire a more concentrated sample for low-level chronic exposures, and the end of the work shift can be more appropriate if the goal of the study is to monitor occupational exposure. Urine serves as a route and medium of elimination for many chemicals, especially nonpersistent chemicals (chemicals with short biologic half-lives); the persistent chemicals are eliminated primarily in feces. The nonpersistent chemicals are generally found in the urine not only

TABLE 4-2 Matrices for Biomonitoring Studies

Collection			Stages of Life				
Matrices	Procedure	Invasive Yes/No	Fetal Period	Delivery	Children 0-5 years old	Children 5-18 years old	Adults
Blood	Venipuncture or prick	Y	–	–	+	+	+
Cord blood	Drained into sterile container from cord after delivery	N	–	+	–	–	–
Urine	Collection cups or diapers	N	–	–	+	+	+
Saliva	Sterile plastic pipette or specially prepared cotton swab	N	–	–	+	+	+
Expired air	Spirometer attachment	N	–	–	+	+	+
Hair	In container after cut or falling out	N	–	–	+	+	+
Fingernails	Clippings in sterile container	N	–	–	+	+	+
Teeth	Collected in sterile container after loss or extraction	N	–	–	+	+	+
Meconium	Collected from diapers	N	–	+	–	–	–
Amniotic fluid	Amniocentesis (mother)	Y	+	–	–	–	–
Adipose tissue	Biopsy or postmortem collection	Y	–	–	+	+	+
Bone marrow	Spinal tap	Y	–	–	+	+	+
Breast milk	Breast pump	N	–	–	–	–	+
Semen	Cup	N	–	–	–	–	+
Feces	Container	N	–	–	–	–	+

as their original "parent" structure but more frequently as metabolites. Urine is an unregulated body fluid, and it varies from void to void in volume and in the concentration of endogenous and exogenous chemicals (Barr et al. 2005a; Wessels et al. 2003). That may be less true of very young children (less than12 months old), because they feed and urinate frequently; but variability in urinary dilution in this age group has not been evaluated. Creatinine adjustment of urinary metabolites has been the standard method for accounting for urine dilution. However, urinary creatinine concentrations vary with age, sex, race and ethnicity, and body-mass index (Barr et al. 2005b). Adjustments of urinary pesticide concentrations with creatinine therefore may not be appropriate in pregnant women and children. A recent study suggests that for multiple regression analyses in epidemiology studies, the analyte concentration unadjusted for creatinine should be included in the model, and urinary creatinine added as a separate independent variable (Barr et al. 2005b).

Blood has inherent advantages for biomonitoring. Regardless of the route of exposure, a chemical must be absorbed into the bloodstream and circulate to the tissues to have an effect (exceptions include direct inhalation effects on the lung and blistering agents on skin) (Needham et al. 2005). Blood is also a "regulated" matrix; therefore, there is a constant amount of blood for a given body weight, so measurements can be "normalized" to this amount. Blood can be collected with vacutainers and other suitable containers without anticoagulant or with heparin, EDTA, or citrate, depending on the types of assays expected to be conducted (Holland et al. 2003). Serum and plasma are most commonly used for measurements of chemicals in blood. Red cells and white cells can be isolated with centrifugation or by using special separation substances (such as Lymphoprep). It is important to decide on the type of vacutainers to be used and the number and volumes of resulting aliquots that will be used for planned analyses without additional freeze-thaw cycles, which may affect sample integrity.

For persistent organic chemicals, a blood sample can be taken years after exposure has occurred. Exposure can still be accurately identified, but the investigator will have no information about when the exposure occurred. Sample collection for nonpersistent-chemical measurements should reflect the residence time of the chemical in each individual matrix. The half-lives of nonpersistent chemicals are typically much shorter in blood than in urine; thus, blood samples may need to be collected within minutes or hours of exposure, whereas urine samples may be collected several hours or even days after exposure (Barr et al. 2005b).

Many other matrices can be used for biomonitoring studies, including saliva, breast milk, hair, fingernails, meconium, bone marrow, and feces (Table 4-2). They differ in level of invasiveness and amounts required for

analysis, which also strongly depend on the stages of life and the types of biomarkers measured. For example, breast milk can contain chemicals from exposures that occurred earlier in a woman's life and thus can reflect cumulative exposure, but measuring these chemicals in her breast milk can be used as a measure of her infant's intake. Investigators have to account for the timing of collection because early milk, called colostrum, significantly differs substantially in content from mature milk. Furthermore, collecting breast-milk samples soon after delivery, although most convenient for the research team, was challenging for mothers in one study (Eskenazi et al. 2005). For most, the milk supply had not yet fully developed, and some new mothers (particularly primiparas) found it difficult to provide samples with a breast pump. In addition, some mothers feared that milk was being taken away from their babies. Later collection of breast milk avoided some of those problems, but timing problems arose for other sample types as well.

Saliva samples typically mimic blood, whereas meconium samples may provide a longer window of time for capturing an exposure.

It is desirable to collect as many different matrices from each study participant as is feasible and to process them with consideration of both immediately planned analyses of biomarkers and future uses. For example, several Children's Environmental Health Centers obtained urine, peripheral blood, cord blood, breast milk, meconium, saliva, hair, placental tissue, infant formula, indoor and outdoor air, and house dust from longitudinal birth cohort studies (Eskenazi et al. 2005). The centers have analyzed concentrations of numerous compounds in those biologic and environmental samples, such as pesticides, phthalates, mercury, lead, cotinine, polycyclic aromatic hydrocarbone (PAHs), PAH-DNA adducts, allergens, endotoxin, antioxidant micronutrients, cholinesterase, and thyroid hormones. Most centers also banked samples for future analyses.

Quality Assurance for Sample Collection

To ensure the quality of specimens for current and future use, most researchers develop protocols for collecting, shipping, processing, and banking samples—standard operating procedures (SOPs) (Heinrich-Ramm et al. 1996; Gunter 1997; Landi and Caporoso 1997; Holland et al. 2003). Pilot studies are conducted to determine the collection and storage conditions necessary for the stability of particular chemicals and their range of concentrations in the cohort. Separating specimens into several aliquots to eliminate the need for repeated thawing and freezing helps to avoid potential contamination and degradation. Field blanks, spikes, and duplicates are included in the analytic batch of samples that are bar coded for making

sample handling less error-prone. Labels include the participant's unique, coded identifier, the sample type, and the aliquot.

A paper trail for each sample is necessary to ensure the integrity of the sample. A complete paper trail includes collection details (date, sample number, type, and volume), shipping information (receipts and tracking numbers), and chain-of-custody forms. In accordance with HIPAA, personal information on the participant must be encrypted. Electronic databases are quickly replacing hard copies, and bar codes allow for quick and accurate encoding and processing of samples.

From Field to Laboratory

Depending on the type of monitoring study, sample collection can take place in the clinic, in the field office, or even in the home of a participant. Each scenario imposes specific requirements and limitations on the type, volume, and potential use of a sample.

Researchers find it helpful to consult with community physicians to determine the amount of blood or other matrix collected that is both clinically and culturally acceptable to the target population (Eskenazi et al. 2005).

Studies conducted in rural areas face additional barriers to successful collection and processing of samples, including laboratory facilities that are inadequately equipped to process samples and a lack of skilled phlebotomists, especially for blood collection from pediatric populations (Eskenazi et al. 2003).

Using noninvasive collection of samples, such as urine, saliva, or exhaled breath tends to increase participation in a study because more participants are willing to subject themselves to a buccal swipe than to a blood draw. When children in one study could not provide urine samples during scheduled visits, investigators gave parents the supplies and instructions to collect the samples at home and arranged to pick them up on the following day (Eskenazi et al. 2003). Noninvasive sample collection also eliminates the need for highly trained personnel to draw blood or perform a biopsy. Some specimens—such as saliva, hair, and nail clippings—can even be obtained by participants at home and mailed to the researcher, making studies in the remote areas more feasible. However, hair and nails are susceptible to contamination in some settings and require specimen consideration in handling.

Sample Stability

Some biomarkers are unstable, so timing of processing, temperature, addition of stabilizing chemicals and buffers, and sterility are important

considerations. Time between collection and processing of a sample is a vital concern. Some processes can be done 24-48 hours after collection; others must be started immediately after collection (Landi and Caporaso 1997). Samples that must be shipped to a processing laboratory cannot be used for the more unstable biomarkers, or processing (including preparing of aliquots, serum and clot separation, and freezing at –80°C) should begin in the field to ensure stability during transportation (Holland et al. 2005).

That different components of blood must be stored at different temperatures should be considered in the study design. Most samples retain their integrity for years if stored in nitrogen tanks (–196°C) or deep freezers (–80°C) (Gunter 1997; Landi and Caporaso 1997). In addition to the preservation of biologic components in the collected samples, it is important to ensure that measurement of environmental pollutants in the samples is not confounded by contaminants in the containers or tools used for sample collection. Prescreening of the materials may be necessary, depending on the toxicant of interest.

Shipping

Sample-shipping requirements depend on the time, distance, climate, season, method of transportation, applicable regulations, type of specimen, and markers to be assessed. Usually, polyurethane boxes containing dry ice are used to ship and transport samples that require low temperatures. The quantity of dry ice should be carefully calculated on the basis of the estimated time of the trip (dry ice evaporates with time, depending on external temperature), the number of samples to be transported in boxes, and an ample safety factor that takes likely delays into account. If the boxes have to be shipped by air, it is suggested that they be placed in the hold of the plane, where the temperature during the trip is very low. Each box should be accompanied by a typed chart describing in detail the contents of the box and the location of each tube in the box. For samples that require very low temperatures, shipping in a liquid-nitrogen container can be optimal.

Communication between field personnel is especially important when samples need to be shipped or transported from the field to the laboratory (Eskenazi et al. 2003). A system of e-mail or telephone messages and confirmations should be established with backup contacts to avoid missed shipments or improper handling on arrival.

Biologic Banks

The main goals of a biologic bank, or biorepository, are to make future analysis of currently unknown biomarkers possible and to minimize research costs of future studies by using previously collected specimens. A

biorepository is "a system which will store one or many types of biologic specimens for later analysis from single or multiple studies under conditions which permit efficient retrieval and optimum stability of the sample" (Winn et al. 1990). Recently, the International Society for Biological and Environmental Repositories published a document that reflects the collective experience of its members with collection and banking of human samples (ISBER 2005); it contains comprehensive information on the handling of blood, urine, nail clippings, saliva, breast milk, and other tissues.

Chapter 2 describes several repositories from completed or current projects in Europe and the United States. The human-matrix repositories vary widely and include commercial banks, national or international project banks, and much smaller biorepositories associated with scientific laboratories or universities. The latter may have 100,000 samples or fewer; larger biorepositories, such as CDC or the National Cancer Institute, have many millions of samples (Gunter 1997; Goodman et al. 2006). Each sample needs to have a secure chain of custody, processing, location, and temperature-stability records compiled in an accessible location. Nanobarcoding and partial to complete automation of a biorepository help to address these issues (Holland et al 2005).

Laboratory Analysis

Laboratory analysis of human specimens is an integral part of any biomonitoring study. Various characteristics of a laboratory method should be evaluated before it is chosen for use in one of the diverse biomonitoring applications discussed in Chapter 3. **Accuracy** reflects the agreement between the measured value and the "true" value. Sources of **bias** or systematic error are numerous. For example, contamination introduced during specimen collection or analysis may bias results upward, whereas incomplete recovery of the analyte from the specimen may bias results toward lower values. Three related terms describe the random variation of data produced from identical specimens. **Precision** is a measure of the degree of agreement among individual results obtained from the same or identical specimens with the same method and by the same analyst and laboratory. Numerous sources of scatter or imprecision exist in laboratory procedures, including random variations in introduced contamination, analyte recovery, and instrument response. **Ruggedness** describes a method's reproducibility under the influence of variation in analyst, instrumentation, day of testing, and laboratory. **Robustness** is a measure of intralaboratory day-to-day variation induced by small changes in procedure. The characteristic of greatest relevance to a given study depends on whether samples are tested in the same or different laboratories, on different days, and so on. The ability to identify and quantify the target analyte in the presence of chemically

similar interfering compounds reflects the **specificity** of the method. Specificity may vary widely between methods on the basis of, for example, the rigor of sample cleanup and the method of instrumental analysis; for example, mass spectrometric detection will typically be more specific than detection by electron capture. A method's **limit of detection** (the lowest concentration that can be measured) also may affect variation. Typically, precision is poorest near the limit of detection. Somewhat arbitrary procedures must be used to "assign" concentrations to specimens whose actual concentrations are below the limit of detection. The results of some statistical calculations, such as the mean concentration in a population, will be influenced by the method used to handle results below the limit of detection, and comparisons between datasets that hold different limits of detection compound the problem (Özkaynak et al. 2005).

In the absence of cost and sample-throughput considerations, users of biomonitoring laboratory data might prefer an analysis that has a limit of detection adequate to measure background exposures, and that can measure the concentration of the target chemical or metabolite with absolute accuracy and precision. Laboratory methods inevitably introduce unwanted error into the dataset, so the last two goals can never be attained. The practical effect of those errors depends substantially on the reason for generating the data. For example, an occupational physician seeking to compare concentrations of a chemical in blood samples drawn from a few employees with national reference values will be concerned about interlaboratory variability but will not necessarily require a very low limit of detection. Alternatively, an epidemiologist conducting a study of an "unexposed" population may require a low limit of detection to classify individual exposure status but, if all samples are analyzed in a single laboratory, may be less concerned about interlaboratory variability introduced by methodologic differences. Study design is important in establishing the optimal balance among variation-related factors.

If an analytic method lacks sufficient specificity, chemical interferences will result in an erroneously high reported concentration. If a measured chemical is introduced as an artifactual contaminant during sample collection or analysis, reported concentrations will also be overestimated. For example, credibly estimating human exposure to phthalates was hindered by the difficulties involved in avoiding specimen contamination with these ubiquitous chemicals; the problem was resolved by focus on the much less prevalent metabolic product, the phthalate half-ester (Silva et al. 2004). Alternatively, a chemical measured as a marker of exogenous exposure may be identical with a chemical formed by an unrelated endogenous metabolic pathway. In each of those cases, a rigorous laboratory-method validation should detect the problem before data are reported. More subtly, the measured biomarker of exposure may be chemically identical with a dietary

chemical not directly relevant to the exposure of interest. For example, organophosphorus-insecticide exposure can be assessed by measuring the metabolic hydrolysis product, the corresponding dialkylphosphate in urine. However, the dialkylphosphate can itself be a dietary component formed by degradation of the parent pesticide in the environment or in a food product (Lu et al. 2005). Under those circumstances, the urinary metabolite may lead to overestimation of exposure to the intact insecticide.

One important characteristic of laboratory-introduced variation is that the expected variation can be statistically defined before an analytic method is first used. A method-validation sequence should be completed before an analytic method is placed into service. Specimens of known concentration are obtained, usually by spiking an appropriate matrix with known concentrations of the target chemical or by using externally provided materials with well-defined and known concentrations. Those specimens are then treated as unknowns and analyzed under conditions closely approximating those to be used in future applications. Thus, depending on study design, the validation specimens might be analyzed by multiple analysts using different instruments on different days. After completion of the validation sequence (which often requires analysis of hundreds of specimens), the resulting data should allow quantitative statements about the expected accuracy, precision, and robustness of the method at multiple concentrations and should establish the method's limit of detection. That information should be provided to the end user of the data because it can influence overall study design (Needham and Wang 2002; Needham et al. 2005).

When the method has been validated and is in regular use, laboratories must maintain rigorous quality-assurance procedures to verify that analysis is being properly performed. Typically, each batch of 10-20 study-related specimens will be analyzed in association with one or two samples of known concentration (either purchased standard reference materials or materials independently prepared by the laboratory): a method blank (a specimen containing an undetectable or very low concentration of the target analyte) and a duplicate. If the results with the quality-control specimens are inconsistent with measurements determined in the validation sequence, the laboratory should investigate the cause of discrepancies, make appropriate corrections, and reanalyze the batch of specimens in question. Those safeguards should ensure that the data quality predicted by the validation sequence is maintained during the analysis of unknown samples.

Participation in interlaboratory comparisons and proficiency-testing programs provides additional information especially pertinent to controlling interlaboratory variation. Aliquots of homogeneous samples containing the analytes of interest are drawn and distributed to each participating laboratory. The participants' results are used to calculate overall and method-specific statistics, such as means, medians, and standard devia-

tions. Such programs allow participants to assess the performance of their laboratory vs those of other participants and encourage laboratories to investigate reasons for any discrepancies observed. Voluntary participation in such programs usually indicates that a laboratory's management is committed to producing high-quality data. In the United States, the federal Clinical Laboratory Improvement Act of 1988 (CLIA-88) requires that any facility that performs diagnostic or treatment-related laboratory testing of human specimens have CLIA approval (Rivers et al. 2005). The CLIA program includes evaluation of staff qualifications, quality-control and quality-assurance (QC-QA) procedures, SOPs, onsite laboratory inspections, and mandatory proficiency testing. However, the current CLIA regulations are not focused on tests relevant to biomonitoring. For example, CLIA recognizes three subspecialties in chemistry (routine chemistry, endocrinology, and toxicology); environmental or occupational chemistry is not a listed subspecialty (42 CFR 493.839 [2005]). Furthermore, CLIA regulations require enrollment in a proficiency-testing program approved by the Centers for Medicare and Medicaid Services (CMS) only for "regulated" analytes. However, the only CLIA-regulated analyte in the chemistry specialty clearly relevant to biomonitoring is blood lead (42 CFR 493.929 [2005]). CLIA requires that laboratories that test analytes not specifically regulated participate in non-CMS-approved proficiency testing, split sampling, or internally generated proficiency tests at least twice a year to demonstrate satisfactory performance (42 CFR 493.1236c [2005]). However, the scarcity of well-validated proficiency tests and interlaboratory comparison studies for unusual or cutting-edge biomonitoring analytes complicates comparison of data generated in different laboratories. The problem may become more acute as the list of chemicals with well-established population-based reference ranges continues to be expanded by the NHANES program, facilitating the interpretation of patient values.

Selecting a laboratory and an analytic method that can provide data of sufficient quality for their intended purpose can be difficult. As a first screen, users of biomonitoring laboratory data should focus on laboratories that systematically work to characterize and minimize laboratory-induced variation. For routinely performed analyses, a laboratory should have completed method-validation sequences and be able to provide statistically based estimates of expected accuracy, precision, limit of detection, and so on. For new methods, the laboratory must conduct an appropriate method validation before initiating sample analysis. The laboratory should also maintain a rigorous QA-QC program to verify that these goals are attained during routine analysis. Particularly when interlaboratory variation can affect data interpretation, the laboratory should participate in available interlaboratory comparisons and proficiency-testing programs. CLIA certification, a legal requirement in the United States for all diagnostic or treatment-related

testing, provides some assurance that test methods are documented and that laboratory staff are appropriately qualified to perform them.

STATISTICAL ANALYSIS

The first principle of analysis is that it follows design. That is particularly true of biomonitoring data. At the beginning of this chapter, we emphasized the importance of describing the selection of the sampled population. Ideally, specific analyses (based on specific hypotheses) have been outlined at the beginning of the study. The statistical jargon phrase for characterizing the sampled population is the *target of inference*. A dataset may have different targets of inference—with resulting differences in the statistical analysis. For example, an occupational physician faced with a specific biomarker concentration in a specific worker is faced with the inferential question of whether the worker belongs to the group of workers "exposed" or "not exposed." The inference will be drawn by bringing in other factors, such as a careful work history. If the same physician is interested in the worker's result for a study of occupational disease, the target of inference is different, and different statistical analyses will be required. Statisticians would couch the first question in terms of fixed-effect analyses and the second in terms of random-effects analyses. Closely tied to the target of inference is the measurement process and its precision. As mentioned previously, if only a single population of inference is of interest, the precision of the measurement is the key driver and sample size determinations should reflect the required precision. If comparisons between two populations are desired, then rather than the precision of the measurements, the magnitude of the difference between the two populations becomes the key driver in the sampling effort.

Before complicated statistical models are constructed and run—increasingly easy with more and more powerful statistical computing packages—it is absolutely necessary to describe the basic characteristics of each variable—number of observations, mean, standard deviation, minimum, and maximum. That will reveal which data are below the limits of detection, are missing, are miscoded, and are outliers. If the study involves three or four key variables, associations among the variables should also be examined. Histograms and scatterplots will reveal data structures unanticipated from the numerical summaries.

If the study is exploratory, it is not uncommon to have a multitude of creative ideas about the nature of the biomarker response and its relationship to the exposure. Ideally, some comparisons of particular interest are specified in advance. The analyses can then be divided into confirmatory and exploratory phases. Two key considerations in such exploratory studies are selection bias and confounding; both were discussed in the section on the sam-

pling of populations, and they should be addressed specifically at the analytic stage. Often, they appear as a throwaway paragraph in the "Study Limitations" section of a paper or a thesis. They deserve a more prominent place.

Longitudinal data are increasingly common. Some of the larger national surveys are considering incorporating longitudinal features. The primary reason is that such approaches can detect shifts more precisely. The Achilles heel of longitudinal studies is missing data. Causes of missing data include death, moving from the area, and refusal to continue with the study. Statisticians have developed a useful terminology for patterns of missingness. Longitudinal data are usually analyzed with fairly complicated statistical models, such as mixed-effect regression models, generalized estimating equations, and logistic-regression models. The validity of a particular model depends heavily on the missing-data pattern. Given that an appropriate class of models has been identified, secondary concerns enter, such as precision of the estimates. The models are not for the statistically naïve, and a professional statistician or someone well versed in the field needs to be consulted. A specific example of longitudinal data involves the monitoring of pesticide handlers in the eastern part of Washington state. The pesticides of concern are cholinesterase inhibitors. A baseline acetylcholinesterase (AChE) concentration is obtained from each handler before the spraying season begins, and handlers are monitored after every 30 hours of handling activity. The end point is AChE depression from baseline expressed as a percentage. If the depression is greater than 20%, specific regulatory actions are begun. The data collected are relevant for each handler but also for the agricultural industry. Issues of false-positive and false-negative depressions also have to be dealt with. In this example, the nature of the missing data becomes very important. Suppose that workers become too sick from the pesticide exposure and simply quit work. This would introduce selection bias. The growers tend to focus on false positives, the workers on false negatives. Resolution of these conflicting aims requires a careful understanding of the within-subject variability and measurement error.

The analyst needs to understand that statistical models vary in their inferential utility. Linear models of some type or other are the most common and the most easily analyzed with statistical computing packages, but they may be only rough approximations of the real world. An oft-quoted aphorism of G.E.P. Box is that "all models are wrong, some are useful." That is no doubt true, but it misses another level of detail of such models as follows. At the simplest level, a model fits the data. At the next level, a model predicts the data. At its most useful level, a model shows unanticipated features of the data and the research, and this is the ideal especially for biomarker research. The most exquisite characterization of association

does not necessarily constitute evidence of causation. As new biomarkers are investigated, the causal link to exposure is a first requirement.

It is usual whenever biologic samples are obtained in medical practice or in any health encounter for results to be expressed in relation to "normal." In fact, a relationship to "normal" is the question almost every subject asks first when presented with such information. For biomonitoring results, it is a generally meaningless question—"normal" for human-made chemicals or chemicals that did not enter the environment except for human activity, is actually zero. Despite that, many laboratories report results, such as blood lead concentrations, in just this way—a practice likely to result in confusion. For example, it is not rare to see reports of blood concentrations that contain the phrase "normal for industrial workers." In truth, such concentrations may be common in industrial workers, or even typical, but hardly normal in the usual meaning of that word in relation to health. Such comparisons are especially problematic for biomarkers whose relationship to health and environmental sources is less well studied. The discussion below touches briefly on the scientific issues raised by such implicit or explicit comparisons of results with reference ranges.

Although the notion of "normal" is not appropriate to biomonitoring, there are two axes of potential reference around which comparisons may be pertinent and indeed important. The first is in relation to comparable subjects. For example, *where adequate information exists*, it would be entirely appropriate to express values in relation to one or more groups of subjects. For example, it would be reasonable to report an individual or group of blood lead concentrations in children as "comparable with those measured (extensively) in populations of children not known to have a specific exposure source" or "suggestive of an identifiable source of exposure." In adults, it might be reasonable to express lead concentrations as "comparable with concentrations seen in the population not occupationally exposed to lead" "within the range of concentrations seen in workers exposed to lead under well-controlled conditions," or the like. Those are not assessments of normality or health effects, merely comparisons with other potentially relevant populations that could lead to research inferences or clinical or public-health interventions.

A second axis for interpretation of results, *relevant only in the small number of situations where information is available to link a biomarker concentration to risk or clinical effects*, is comparison with such risk or health-effect concentrations, for example, at or below the concentrations previously associated with developmental delays in children. The point is that the health comparison must be explicit and referenced to the source of the inference, such as an epidemiologic study or reference publication.

SUMMARY AND CONCLUSIONS

Biomonitoring challenges laboratory methods, ethical considerations, and communications strategies. It also challenges the technical limits of epidemiology and biostatistics. This chapter has provided guidelines for the conduct of biomonitoring studies, including study design, study conduct, and data analysis. Because not all biomonitoring studies are conducted with the same rigor, it is important that the guidelines presented be followed to ensure, to the extent possible, that biomonitoring studies will lead to the identification of chemicals that are causing risks or health effects, will provide information on exposure pathways and health effects to guide future control efforts, and will avoid anxiety or apathy about chemicals where personal or societal risk appears not to warrant that reaction.

Wherever blood or other matrices are being collected from a sample of any population—whether for surveillance, etiologic study, or clinical evaluation—the highest standards of sampling theory should be adhered to, and the approach should be explicitly described in publications and reports so that biases may be recognized. If it is feasible, results should be expressed in terms not only of age groups, sex, and race, but also in relation to quantifiable lifestyle factors, such as occupation, income, and education.

A great deal of effort and time is involved in getting studies approved. Hence, it is absolutely essential to address questions of ethics at the design stage. Informed consent and IRB approval became especially important when more than one research site or jurisdiction is involved, as this can introduce a problematic cycle of approval at one level and modification at another. Because the value of biomonitoring in the long run is the ability to link the sample result back to human health and risk factor information, the links between the biomonitoring and health data should not be severed, while at the same time ensuring confidentiality of the data.

A topic linked to ethics but with its own issues and strategies is communication. The committee is convinced that communication starts with the study proposal and continues through study design. Each of the many constituencies associated with a proposed study requires careful consideration in planning communication strategy and content. Most biomonitoring studies will eventually have applications, and researchers need to anticipate potentially affected communities and plan for communication with them.

A carefully, comprehensively designed study facilitates study conduct. Two key elements of study conduct are sample collection and laboratory analysis. The choice of matrix depends on both theoretical and practical considerations. Those include the tissue most likely to represent the biomarker route of exposure and the ease of obtaining samples. Careful attention to collection and shipping from field to laboratory is a prerequisite for valid laboratory analysis. The choice of analytic laboratory methods is

determined by cost, sensitivity, and specificity. Quality control surrounds both the collection and the laboratory analysis of samples.

Analysis of biomonitoring data, following the strategies initiated in study design, begins with description of the data in ways that are transparent. Sources of a priori importance and those introduced by random variation must be explicitly addressed in any statistical model, as must the context for tests of statistical significance. In every case, diligent attention to noncausal relationships within the data—associations due to bias and confounding—demand the greatest professional attention because such spurious associations are likely when so many chemicals are studied, and hypotheses remain so open-ended. Data analysts should approach results mindful that for the vast majority of biomarker measurements, results can neither be claimed to be normal in the usual sense—zero is probably the original human condition for most—nor be assigned value judgments, such as "high." Any such designations should emerge from the interpretation of the data in context, not from the results of a single individual study or survey.

RECOMMENDATIONS

- A biomonitoring-study report should contain a detailed description of the origin of the sample of subjects selected for study. The vast majority of biomonitoring studies are not based on a CDC-like probabilistic sample of the population. Investigators should state explicitly the population that their results apply to. Editors of journals should insist that this information be included in any submission.
- Any analysis of biomonitoring data should include an assessment of the importance of sources of variation. Basic sources to be considered are laboratory, intra-individual, interindividual, and variability attributable to groups.
- Great effort should be made to develop a human pharmacokinetic, preferably PBPK, model early in the study-design process. The likely influence of, for example, model simplification (for example, assuming a single half-life), metabolic saturation, and influence of sampling time may then be addressed before spending vast resources on sampling and analyses. By adding statistical tools (Monte Carlo simulation, population models) to the model, additional features may be examined including variability in exposure pattern and intra- and interindividual variability in pharmacokinetic determinants.
- Investigators, including CDC, that conduct surveys of biomarkers in the population should routinely collect detailed information about SES, lifestyle, and other cofactors on each subject and should routinely present results organized in a way that addresses the issue of whether biomarker concentrations vary as a function of each. Epidemiologic analyses of bio-

markers in relation to health should routinely include appropriate adjustments for such covariates.

- Incorporating communication in the design of a biomonitoring study is essential. The type of communication needed will depend on the goals of the biomonitoring study. Careful attention to planning effective communication at the beginning of a biomonitoring study will make communication at the end of the study easier and may make the technical aspects of the study proceed more smoothly. Biomonitoring funders should require communication planning in any application for support.
- Research is needed to develop and disseminate effective methods for evaluating communication of study results.
- With respect to providing information to study participants, the committee considers that failing to provide detailed information about all biomarkers to be measured, no matter how many chemicals are involved in the study, raises ethical questions.
- Blanket consent for use of biomonitoring samples at some future time has the potential to result in abuse. However, there are practical difficulties in repeated tissue sampling that the absence of blanket consent reinforces. Research is needed to develop new approaches for obtaining consent for future uses of biomonitoring data.
- Biologic and environmental specimens should be carefully collected with rigorous QA-QC provisions and should be processed and banked in multiple aliquots with comprehensive characterization of their origin and history.
- Laboratory analysis of human samples for trace contaminants or their metabolites inevitably produces results that deviate quantitatively from the actual concentrations. Such deviations can, for example, complicate exposure classifications in epidemiologic studies, detection of time trends in exposure, and comparison of studies that use data produced with different analytic methods. Individual laboratories can use standard QA-QC methods to minimize and define the magnitude of the variations. However, federal agencies and statutes, such as CDC, the National Institute of Standards and Technology, and statutes such as CLIA, could play important roles in improving the overall quality of biomonitoring laboratory data and their utility in health-related applications.
- NHANES and other studies are rapidly expanding the list of chemicals for which population-based reference values are available. Health practitioners will increasingly seek to compare data from potentially occupationally or environmentally exposed patients with those reference values. That application requires consistency between data generated from different laboratories. CMS, through the CLIA program, regulates clinical-laboratory testing for nonresearch-related purposes. However, the program does not emphasize testing for chemicals associated with environmental or occupational

exposure. The quality of such data would be improved if CMS created a new chemistry subspecialty related to environmental and occupational medicine and expanded the array of regulated analytes supplied by approved proficiency-test providers.

- It is essential to develop and use noninvasive and ultrasensitive specimen-collection techniques for the biomonitoring of children and other groups that can provide only small samples.
- Researchers should anticipate maintenance of samples in biorepositories (banks) for future generations of researchers. Such banking requires attention, at the planning and design stages, to ethical considerations, communication strategies, location and storage of samples, and—last but not least—the costs involved.
- As soon as practicable, researchers should standardize and harmonize biomonitoring measurements to make scientific communication feasible. That may involve the development of reference materials that can be shared among laboratories. Standardization and harmonization are particularly important for international collaboration.

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5

Interpretation of Biomonitoring Results

INTRODUCTION

Finding chemicals in bodily fluids is evidence of contact with them through inhalation, dermal exposure, or ingestion, and it typically leads to two questions that pose important challenges in interpreting biomonitoring results and are the focus of this chapter:

- Is the biomonitoring result in a range that is typical of the general, non-occupationally exposed population?
- Does the biomonitoring result indicate a health risk?

This chapter describes various options for interpreting biomonitoring results with respect to those two questions and discusses how the analysis and interpretation can be used in different biomonitoring settings. The settings in which biomonitoring results may need interpretation include the workplace, the doctor's office, screening of the general population, and study of specific subpopulations. The purpose and use of biomonitoring data may vary among those scenarios, but the options for interpreting the data are generally similar.

Other questions that are alluded to but not addressed in detail in this chapter include, how did the exposures occur? Are there means to decrease the exposures? These questions involve interpretation of biomonitoring data but also extend into risk-management issues.

Figure 5-1 is a flow diagram of the information provided in this chapter. When biomonitoring data become available, one must determine the

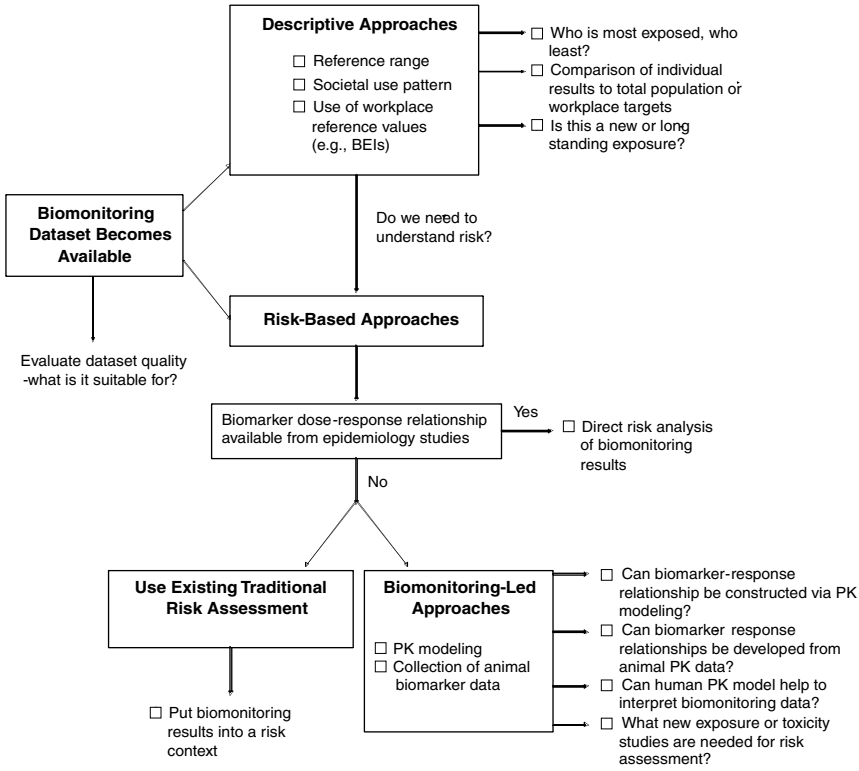

FIGURE 5-1 Overview of interpretive options for biomonitoring data.

interpretive options for evaluating them. The options include descriptive approaches that involve comparisons among biomonitoring datasets and risk-based approaches that describe the degree of risk associated with a given biomonitoring result. Throughout this chapter and in Appendix B, case studies are used to illustrate the applications of biomonitoring data to understanding of risk. The case studies are intended solely as illustrations and are not judgments about the data or risks associated with the chemicals discussed.

INITIAL REVIEW OF BIOMONITORING DATA

Interpreting biomonitoring results depends on the availability of various types of information, including data on exposure, toxicity, and toxicokinetics. If toxicity information is unavailable, the results cannot be put into a risk

context. If exposure information is unavailable, it may not be possible to determine where and how the exposures that produced the measured biomarker concentrations occurred. However, the starting point for interpreting biomonitoring data is an assessment of the quality of the biomonitoring data. If they are of low quality, there is little point in considering whether exposure or toxicity information is available. But high-quality biomonitoring data may be applied to a variety of interpretive options, as outlined below. Chapter 4 reviews the considerations relevant to the design of biomonitoring studies to ensure scientific quality and integrity.

OVERVIEW OF INTERPRETIVE OPTIONS FOR BIOMONITORING DATA

Two main options for interpreting biomonitoring results—descriptive and risk-based approaches—appear in Figure 5-1. This figure is organized from simplest to most complex approaches, with the potential for interpreting health risks also increasing from top to bottom. The expectation is that the quicker, descriptive approaches would be used first and then, depending on the level of concern and data availability, risk-based approaches would be used. The final interpretation of biomonitoring data would probably have elements of both.

Descriptive Approaches

The first level of analysis is purely descriptive, presenting a statistical review of the data, typically in the form of a data distribution from which percentiles of the population (such as 10th, 25th, 50th, 75th, and 90th percentiles) are easily obtained. That establishes a reference range with which individual or subgroup results can be compared. The range offers a point of comparison; individuals or subgroups may be within the range or may be subject to more or less exposure or vulnerability. A number of interpretive issues in this approach are described in this chapter. For the most part, the Centers for Disease Control and Prevention (CDC) analysis of biomonitoring results from its National Health and Nutrition Examination Survey (NHANES) is focused on the reference-range approach (CDC 2005).

Another descriptive approach characterizes a chemical's use pattern in society at large. The information is used to interpret biomonitoring data in terms of how long the chemical may have been detected in bodily fluids and whether its concentration may be going up or down with changing use. It is not uncommon for the public to consider a new biomarker as evidence of new exposure. But it is possible that exposure has been going on for de-

cades and the biomarker became available only recently. Because new or increasing exposure generally prompts greater concern, the context is important. This question is best answered by analysis of biomonitoring results that span several years of sample collection. However, if biomonitoring results are available only for a single sampling round, temporal trends cannot be known. In such a case, historical data on chemical production rates and trends may be useful (if they are available).

Workplace biologic reference values are another descriptive option for interpreting biomonitoring results in the general population. Such values as the Biological Exposure Index (BEI) of the American Conference of Governmental Industrial Hygienists (ACGIH) are workplace standards used to evaluate whether individual workers have received exposures that exceed a workplace air standard, such as a Threshold Limit Value (TLV). A blood or urinary biomarker is a better indication of personal exposure than an area air sample. BEIs have been used as points of reference for biomonitoring results in the general public (CDC 2005). However, because BEIs do not take into account the differing exposure patterns (continuous vs 8-hour workshift exposure) and vulnerability of the general public (including children, pregnant women, the elderly, and the ill) compared with healthy workers, using BEIs to judge community exposure and risk raises numerous interpretive issues. This chapter reviews those issues and outlines major limitations in applying adjustment factors to BEIs to derive biomarker targets relevant to the general public.

Risk-Based Approaches

The most data-intensive approaches are those which evaluate the risk associated with a biomonitoring result. Evaluation of risk may be a desirable outcome, given the importance of the "How risky is this blood concentration" question and the fact that the descriptive approaches only provide relative information and do not assess risk. Figure 5-2 illustrates the various risk-based options discussed in the report.

In the most straightforward risk-based approach, epidemiologic studies have developed exposure-response relationships based on biomarker measurements in hair, blood, urine, or other matrices (e.g., mercury, lead) (see Figure 5-2a). The relationships can be applied directly to new biomonitoring data to determine where on the exposure-response curve any person is. That may facilitate an understanding of risk, but it does not analyze sources of exposure, so other techniques (such as environmental sampling and behavioral surveys) may be needed to assess where the exposure came from.

Because human biomarkers are rarely the basis of exposure-response relationships, practitioners generally rely on more traditional risk assess-

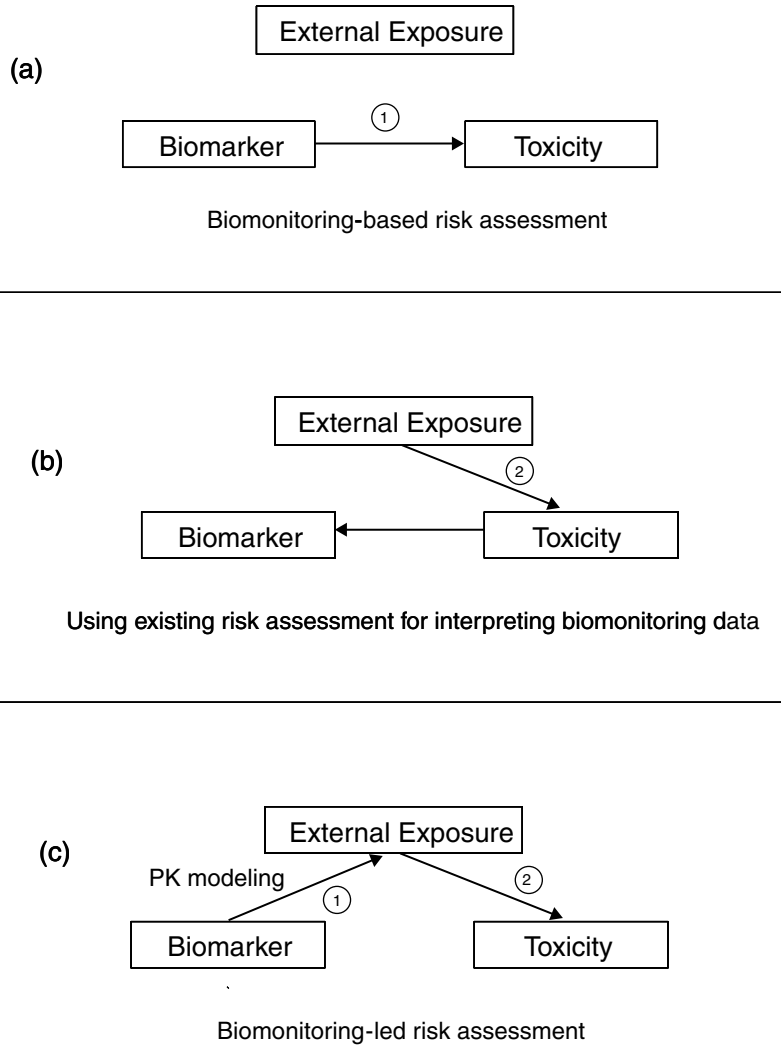

FIGURE 5-2 Illustration of the interpretative risk-based options.

ments. Those assessments characterize human exposure with a pathways analysis, accounting for concentrations in air, food, water, and soil to estimate human dose in milligrams per kilogram per day. The dose is then used to calculate risk on the basis of reference doses or cancer slope factors (see Figure 5-2b). Using existing risk assessments for interpreting biomonitoring data can help to put biomonitoring results into a broad risk

context that makes maximal use of the underlying exposure and toxicology data but falls short of actually calculating risk.

Another option attempts to convert biomonitoring results into a form that is directly useful for risk assessment. The chapter describes both the human pharmacokinetic (PK) modeling used to relate internal concentration to dose and the development of exposure-response relationships in animal studies that use biomarker concentrations rather than applied dose (see Figure 5-2c). Finally, the chapter describes how biomonitoring studies can augment and help to interpret traditional risk assessments.

Many communication challenges stem from collection, interpretation, and reporting of biomonitoring results. This chapter indicates where communication issues arise in relation to the interpretation of biomonitoring results; these issues are explored more fully in Chapter 6.

Case Examples Used in This Chapter

A number of case examples are used to illustrate the feasibility of the interpretive options described in this chapter. Some of the examples are presented in the chapter, and others are presented in Appendix B. Generally, examples were selected because they have the requisite data from epidemiology, PK, or animal toxicology studies to facilitate the risk interpretation of biomonitoring results. For many other chemicals that may be the subjects of biomonitoring, those types of data are not available and thus constitute biomarker-specific data gaps. Such data gaps need to be filled case by case on the basis of the type of biomarker and the underlying database to improve our interpretation of biomonitoring results. As exemplified by the examples presented, it may be most expeditious in some cases to obtain animal PK and in others to use human PK modeling or epidemiology studies (Table 5-1). However, obtaining data may take months. Some of the recommendations presented by the committee in Chapter 7 attempt to address the biomarker data gaps through a research agenda.

When data gaps are filled, there may be disagreement about how to apply the data for interpreting biomonitoring results. For example, the biomarker–toxicity relationship for methylmercury has been controversial because of the differences in results among major epidemiology studies (Appendix B). Although a national consensus has emerged after the National Research Council review of methylmercury (NRC 2000), there may not be an opportunity for such a comprehensive analysis of other biomarkers as data gaps are addressed and risk assessors use existing data.

The case studies in this chapter and in Appendix B are presented to illustrate particular points and are not intended to be exhaustive in their review or analysis of a chemical.

TABLE 5-1 Overview of Major Biomarker Case Examples Used to Illustrate Interpretive Options

Chemical	Biomarker	Interpretive Option Exemplified	Where Presented
PBDE	PBDEs in blood and breast milk	Biomonitoring studies demonstrate key data gaps; need to obtain new toxicity and exposure information	Chapter 5
Organophosphates	Various metabolites	Comparison of subpopulation with reference range	Chapter 5
Glyphosate	Urinary glyphosate	Use of existing risk assessment to put biomonitoring results into risk context	Appendix B
Permethrin	Urinary carboxylic acid metabolite	Use of existing risk assessment to put biomonitoring results into risk context	Appendix B
TCE	Blood TCE	Use of Bayesian techniques and bounding approaches to estimate exposure dose from non-steady-state blood concentration	Appendix B
PFOA	Serum PFOA	Use of animal toxicology and physiologically based pharmacokinetic modeling to develop biomarker-response relationship in animals	Chapter 5
Lead	Blood lead	Use of epidemiology studies to develop biomarker-response relationship in humans	Chapter 5
Mercury	Blood mercury	Use of epidemiology studies to develop biomarker-response relationship in humans	Appendix B
Chlorpyrifos	Urinary TCP	Use of pharmacokinetic modeling to estimate exposure dose from amount excreted in urine	Appendix B
Phthalates	Urinary monoester metabolites	Use of pharmacokinetic modeling to estimate exposure dose from amount excreted in urine	Chapter 5
Dioxin	Dioxin in blood or lipid	Use of pharmacokinetic modeling to estimate body burden and daily dose	Appendix B
Styrene	Urinary metabolites	Use of worker urinary metabolite-exposure information to develop pharmacokinetic model applicable to general public	Appendix B

Abbreviations: PBDE = polybrominated diphenyl ether; TCE = trichloroethylene; PFOA = perfluorooctanoic acid; TCP = trichloro-2-pyridinol.

REFERENCE RANGES

Biomonitoring results can be interpreted at different levels of complexity (Figure 5-1). The reference-range approach represents the least complex level. It is only descriptive, offering a statistical presentation of data (Tables 5-2 and 5-3) for comparison with data from other populations or individuals but with no conclusions about risk potential. However, this approach is often the first stage in the more complex risk-related analyses discussed in the remainder of the chapter.

In the reference-range approach, reference ranges (or intervals),[1] are established, and biomonitoring values from individuals or subgroups are compared with them. The validity and utility of biomonitoring values for use as reference ranges depends on study design and data quality, with special attention to the availability and comparability of data on the reference population in relation to the study population.

The overview below focuses on two fundamental elements of the reference-range approach: establishing a reference range and interpreting biomonitoring data in comparison with it. The remainder of this section details methods, principles, and issues related to data quality and reference-population selection and comments on regulatory uses of this approach and related cautions.

Overview

Establishing Reference Ranges

Recent biomonitoring efforts in the United States and Europe have placed a high priority on establishing reference ranges. For example, a central purpose of the *Third National Report on Human Exposure to Environmental Chemicals* (CDC 2005) is "to establish reference ranges that can be used by physicians and scientists to determine whether a person or group has an unusually high exposure." The report updates and supplements two earlier reports (CDC 2001, 2003). As documented in Chapter 2, other nations and international organizations are developing comparable information.

The CDC sampling plan follows a "complex, stratified, multistage, probability cluster design to select a representative sample of the civilian noninstitutionalized population of the United States." Relevant details are

[1]Poulsen et al. (1994) appear to use the term *reference interval* as synonymous with *reference range*. In a paper titled "Trace element reference values . . . ," the authors emphasize that "knowledge of the reference intervals (baseline data) for the trace elements in human body fluids and tissues is of paramount importance."

TABLE 5-2 Blood Concentrations for Cadmium in the U.S. Population Aged 1 Year and Older

	Survey Years	Geometric Mean (95% confidence interval	Selected Percentiles[a] 50th
Total, age 1 year and older	1999-2000	**0.412** (0.378-0.449)	**0.300** (0.300-0.400)
	2001-2002	*b*	**0.300** (<LOD-0.300)
Age group			
1-5 years	1999-2000	*b*	<LOD
	2001-2002	*b*	<LOD
6-11 years	1999-2000	*b*	<LOD
	2001-2002	*b*	<LOD
12-19 years	1999-2000	**0.333** (0.304-0.336)	**0.300** (<LOD-0.300)
	2001-2002	*b*	<LOD
20 years and older	1999-2000	**0.468** (0.426-0.513)	**0.400** (0.300-0.400)
	2001-2002	*b*	**0.300** (0.300-0.400)
Sex			
Male	1999-2000	**0.403** (0.368-0.441)	**0.400** (0.300-0.400)
	2001-2002	*b*	**0.300** (<LOD-0.300)
Female	1999-2000	**0.421** (0.386-0.460)	**0.300** (0.300-0.400)
	2001-2002	*b*	**0.300** (0.300-0.400)
Race or ethnicity			
Mexican Americans	1999-2000	**0.395** (0.367-0.424)	**0.400** (0.300-0.400)
	2001-2002	*b*	<LOD
Non-Hispanic blacks	1999-2000	**0.393** (0.361-0.427)	**0.300** (0.300-0.400)
	2001-2002	*b*	<LOD
Non-Hispanic whites	1999-2000	**0.420** (0.376-0.470)	**0.400** (0.300-0.400)
	2001-2002	*b*	<LOD

[a]LOD = limit of detection, which may vary for some chemicals by year and by individual sample.
[b]Not calculated. Proportion of results below limit of detection was too high to provide valid result.
Source: CDC 2005.

developed in Chapter 4. The monitored populations are in broad groups defined by age, sex, and race or ethnicity. Data are analyzed and presented in eight main categories: 6-11 years old, 12-19 years old, over 20 years old; males, females, Mexican Americans, non-Hispanic blacks, and non-Hispanic whites. Other racial groups are sampled as part of the total population but do not make up a large enough proportion of the total to provide valid estimates. Newborns and infants are not included, because of difficulties (such as parental resistance and sample size) in obtaining biomonitoring data for these age groups.

(in mg/L) (95% confidence interval)

75th	90th	95th	Sample Size
0.600 (0.500-0.600)	**1.00** (0.900-1.00)	**1.30** (1.20-1.40)	7,970
0.400 (0.400-0.500)	**0.900** (0.900-1.10)	**1.30** (1.20-1.60)	8,945
0.300 (<LOD-0.300)	**0.400** (0.300-0.400)	**0.400** (0.300-0.400)	723
<LOD	<LOD	**0.300** (<LOD-0.300)	898
0.300 (<LOD-0.300)	**0.400** (0.300-0.400)	**0.400** (0.400-0.500)	905
<LOD	<LOD	**0.400** (0.300-0.400)	1,044
0.300 (0.300-0.400)	**0.800** (0.600-0.900)	**1.10** (0.900-1.10)	2,135
0.300 (<LOD-0.300)	**0.400** (0.400-0.500)	**0.800** (0.600-1.10)	2,231
0.600 (0.600-0.700)	**1.00** (1.00-1.10)	**1.50** (1.40-1.60)	4,207
0.600 (0.500-0.600)	**1.10** (0.900-1.20)	**1.60** (1.30-1.80)	4,772
0.600 (0.500-0.600)	**1.00** (0.900-1.10)	**1.30** (1.20-1.50)	3,913
0.400 (0.400-0.500)	**0.900** (0.900-1.10)	**1.40** (1.20-1.80)	4,339
0.600 (0.500-0.600)	**1.00** (0.800-1.00)	**1.30** (1.10-1.40)	4,057
0.500 (0.500-0.600)	**1.00** (0.900-1.10)	**1.40** (1.20-1.60)	4,606
0.400 (0.400-0.500)	**0.700** (0.700-0.900)	**1.10** (0.900-1.30)	2,742
0.300 (0.300-0.400)	**0.600** (0.500-0.700)	**1.00** (0.700-0.900)	2,268
0.600 (0.500-0.600)	**1.00** (0.800-1.10)	**1.40** (1.10-1.50)	1,842
0.400 (0.400-0.500)	**1.00** (0.900-1.00)	**1.40** (1.20-1.50)	2,219
0.500 (0.500-0.600)	**1.00** (0.900-1.10)	**1.30** (1.20-1.40)	2,716
0.500 (0.500-0.600)	**0.900** (0.900-1.10)	**1.40** (1.20-1.80)	3,806

As shown in Tables 5-2 and 5-3, the data on each group include survey period, geometric mean, population sample size, and the biomarker concentration at the 50th, 75th, 90th, and 95th percentiles of the population distribution.

Comparison with a Reference Population

At the simplest level of interpretation of biomonitoring data, a biomarker concentration found in an individual or group under study is com-

TABLE 5-3 Urine Concentrations for Cadmium in the U.S. Population Aged 6 Years and Older

	Survey Years	Geometric Mean (95% confidence interval	Selected Percentiles[a] 50th
Total, age 6 years and older	1999-2000	**0.193** (0.169-0.220)	**0.232** (0.214-0.249)
	2001-2002	**0.210** (0.189-0.235)	**0.229** (0.207-0.255)
Age group			
6-11 years	1999-2000	[a]	**0.078** (0.061-0.101)
	2001-2002	**0.061** (<LOD-0.081	**0.077** (0.067-0.092)
12-19 years	1999-2000	**0.092** (0.067-0.126)	**0.128** (0.107-0.148)
	2001-2002	**0.109** (0.087-0.136)	**0.135** (0.114-0.157)
20 years and older	1999-2000	**0.281** (0.253-0.313)	**0.306** (0.261-0.339)
	2001-2002	**0.273** (0.249-0.299)	**0.280** (0.261-0.308)
Sex			
Male	1999-2000	**0.199** (0.165-0.241)	**0.227** (0.193-0.263)
	2001-2002	**0.201** (0.177-0.229)	**0.223** (0.191-0.257)
Female	1999-2000	**0.187** (0.153-0.229)	**0.239** (0.220-0.255)
	2001-2002	**0.219** (0.192-0.251)	**0.234** (0.202-0.265)
Race or ethnicity			
Mexican Americans	1999-2000	**0.191** (0.157-0.233)	**0.202** (0.167-0.221)
	2001-2002	**0.160** (0.135-0.189)	**0.181** (0.171-0.198)
Non-Hispanic blacks	1999-2000	**0.283** (0.208-0.387)	**0.312** (0.243-0.412)
	2001-2002	**0.277** (0.229-0.336)	**0.302** (0.257-0.354)
Non-Hispanic whites	1999-2000	**0.175** (0.148-0.206)	**0.220** (0.194-0.246)
	2001-2002	**0.204** (0.179-0.231)	**0.221** (0.191-0.255)

[a]Not calculated. Proportion of results below limit of detection was too high to provide valid result.
Source: CDC 2005.

pared with that in a reference population. That approach depends on a suitable reference population and a body of biomonitoring data collected in comparable fashion that can serve as a reference range. (For discussion of an appropriate comparison population, see Chapter 4.)

Figure 5-3 illustrates the distribution of biomarker concentrations in a generic reference population, expressed as cumulative frequency. As is commonly done in a clinical test, the 95th percentile of the distribution can be used to determine the upper limit value of this test result. However, a different percentile may be chosen, depending on the circumstances, the characteristics of the reference population, the distribution of the results, and the intended purpose of the study. It is important to be aware that a particular cut point does not represent a bright line that automatically separates the population into typical vs highly exposed, or no risk vs high risk (when, for example, BEIs or risk-based targets are used). Rather, it is a guideline to point out where in the population distribution exposures may require more detailed analysis of sources and health risks.

(in mg/L) (95% confidence interval)			
75th	90th	95th	Sample Size
0.475 (0.436-0.519)	**0.858** (0.763-0.980)	**1.20** (1.06-1.33)	2,257
0.458 (0.423-0.482)	**0.839** (0.753-0.919)	**1.20** (1.07-1.28)	2,690
0.141 (0.115-0.173)	**0.219** (0.178-0.233)	**0.279** (0.211-0.507)	310
0.140 (0.112-0.160)	**0.219** (0.184-0.262)	**0.282** (0.260-0.326)	368
0.202 (0.183-0.232)	**0.329** (0.272-0.372)	**0.424** (0.366-0.596)	648
0.210 (0.189-0.247)	**0.327** (0.289-0.366)	**0.442** (0.366-0.480)	762
0.551 (0.510-0.621)	**0.979** (0.836-1.13)	**1.31** (1.13-1.57)	1,299
0.545 (0.493-0.607)	**0.955** (0.855-1.06)	**1.28** (1.20-1.43)	1,560
0.462 (0.381-0.539)	**0.892** (0.748-1.15)	**1.41** (0.980-1.83)	1,121
0.445 (0.393-0.481)	**0.870** (0.741-1.03)	**1.22** (1.12-1.38)	1,335
0.492 (0.456-0.540)	**0.806** (0.705-0.980)	**1.10** (1.01-1.19)	1,136
0.466 (0.433-0.519)	**0.817** (0.733-0.886)	**1.17** (0.918-1.36)	1,355
0.438 (0.351-0.551)	**0.813** (0.686-0.977)	**1.12** (0.886-1.38)	780
0.321 (0.285-0.362)	**0.559** (0.430-0.733)	**0.766** (0.633-1.15)	683
0.633 (0.498-0.806)	**1.22** (0.892-1.38)	**1.48** (1.30-1.72)	546
0.580 (0.476-0.713)	**1.04** (0.843-1.38)	**1.51** (1.28-1.74)	667
0.455 (0.388-0.510)	**0.797** (0.714-1.01)	**1.17** (0.963-1.47)	760
0.445 (0.394-0.479)	**0.813** (0.717-0.875)	**1.17** (0.989-1.24)	1,132

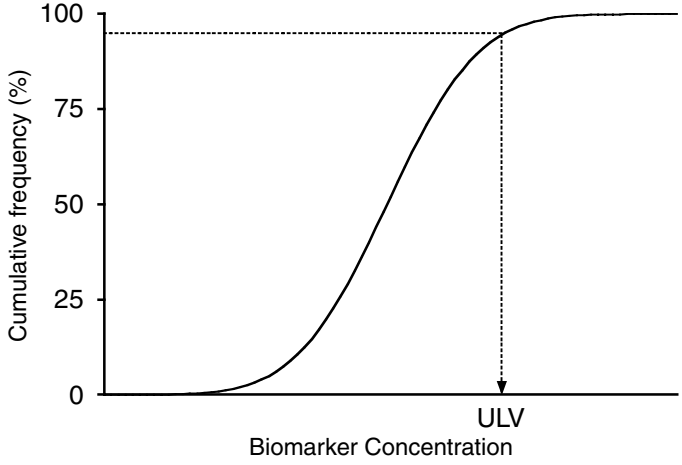

FIGURE 5-3 Distribution of biomarker concentrations in generic reference population. ULV is the upper limit value.

Thus, although the 95th percentile is commonly used and provides a convenient reference value, a variety of factors recommend case-by-case attention to cut-point selection. In a distribution influenced by unique but low percentage subgroups, the 95th percentile may include a unique subgroup that is distinct from the remainder of the population in PK factors. Those factors may lead to much higher internal concentrations than the central tendency. To include such a group in the reference range would encourage an analyst to overlook important heterogeneity in the population. If a subgroup is large enough to cause the overall distribution to be bimodal, a reference range for each group may be needed to characterize the population fully. In that case, the internodal or inflection point is a critical value that distinguishes subpopulations.

Finally, if the 95th percentile is highly unstable or uncertain because of high variability (for example, if the distribution has a long tail), a more stable percentile would be preferable.

Comparison with a reference range is useful for all applications in which a reference population is available. In the workplace, one may be able to identify high-exposure job categories by using biomonitoring results and evaluate whether measures to mitigate exposure are working to bring subgroups back toward the reference range. Air monitoring may also be helpful in that regard. Establishing a reference range for the general population can help in interpreting the results on an individual subject by assessing where on the results distribution the person lies. Results near or below the median suggest that exposure is not particularly high in relation to everyone else's. Some people will be at the upper end of the distribution and lie outside the reference range. It may be important to identify and study them further to determine the characteristics (such as location of dwelling, product use, and other personal behaviors) and physiologic factors (such as genetic polymorphisms) that caused the high exposures. It may be equally valuable to understand why other people lie at the lower end of the distribution; such information may offer lessons in controlling exposure to some chemicals. Unfortunately the tendency is for biomonitoring studies to highlight central tendency and upper-bound statistics and not to report the lower end of the distribution. Therefore, researchers may overlook individuals who are important to evaluate because of either low exposures or genetic factors that favor chemical clearance.

Pertinent to the above comparisons is the assumption that the data are from a single study that used a uniform sampling design and method, which initially treated the sampled group as a single population. However, biomonitoring can also study subgroups suspected of having unique exposures—for example, because they lived next to a potential source—in a cross-sectional design. Those results can be informative when compared with the reference range and can help to answer the question of whether a

BOX 5-1
Case Example: Organophosphorus Metabolites in Pregnant Farm Workers

A recent report illustrates the utility of the reference-range approach. In a study designed to collect descriptive information on urinary concentrations of organophosphorus (OP) metabolite during and soon after pregnancy, Bradman et al. (2005) collected samples from 600 pregnant low-income women living in California's Salinas Valley. Some 28% were employed as farm field workers during pregnancy. For 81% of these women, at least one member of their household worked in agriculture.

In addition to providing comparative antepartum and postpartum OP metabolite concentrations in the study population, the study compared data in these women with data on women 19-40 years old in the general U.S. population surveyed for the Second National Exposure Report (NHANES) (CDC 2003). The investigators reported that pregnant women living in an agricultural area had higher concentrations of the metabolites than the general U.S. population. Used in that way, the biomarker exemplifies the type of comparative information that can be obtained with what Chapter 3 classifies as a category II biomarker (a reliable method for indexing internal exposure and useful for characterizing reference ranges and comparisons among population groups).

suspected contaminant source is, in fact, leading to increased exposures and body burden. Box 5-1 presents a case example of the utility and limitations of reference ranges.

Methodology, Principles, and Issues

Ideally, reference ranges consist of biomonitoring values developed according to scientifically rigorous study design and quality-control procedures (see Chapter 4). The utility of reference ranges depends on attention to reference populations and data quality.

Reference Populations

The reference-range approach depends on data *availability* and data *comparability* for both the *reference* and *test* populations. Ideally, the two populations are comparable in age, race or ethnicity, sex, and other demographic factors and were analyzed for the same end point in the same tissues or fluids (see introduction to this chapter and Chapter 4).

Interpreting biomonitoring data from individuals or groups depends on the characteristics of the reference group (Viau et al. 2000). The importance of comparability cannot be overstated. For example, comparative data on

urinary 1-hydroxypyrene (1-OHP) in a rural population in Burundi suggest that it might be more relevant to compare this population with other inhabitants of Burundi—even urban residents living in the capital, Bujumbura—than with an urban population in North America. There may be any number of reasons for this, such as more comparable lifestyle and exposures within a country than between continents and greater relevance for interpreting the opportunity for public-health intervention within a country. As shown in Figure 5-4, the rural population of this study (no occupational exposure) excreted considerably more 1-OHP than did the in-country urban reference group and as much urinary 1-OHP as some populations of workers in the creosote industry (data not shown). The rural population had no occupational exposure but was heavily exposed to polycyclic aromatic hydrocarbons (PAHs) through the use of indoor wood-burning for cooking purposes. A different type of comparison could be made among

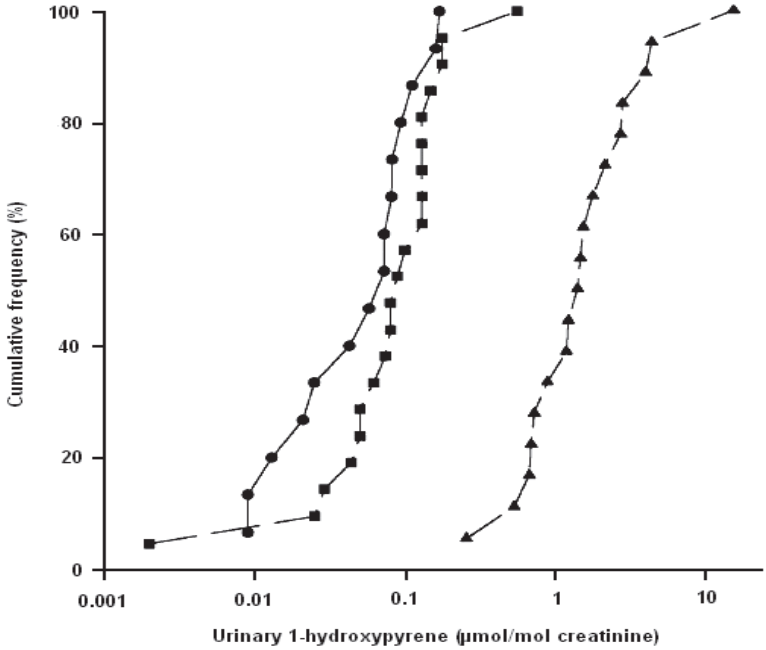

FIGURE 5-4 Cumulative frequency distribution of the urinary excretion of 1-hydroxypyrene in people living in two rural districts of Burundi (▲), in Bujumbura (●) and in a reference group at the University of Montreal (■). Source: Viau et al. 2000. Reprinted with permission; copyright 2000, International Archives of Occupational and Environmental Health.

urban residents between continents (Bujumbura vs North American populations). In other words, the reference group must always be selected on the basis of the study's objectives and a priori knowledge of exposure of the reference group.

In addition, information is needed on the history of exposure to the parent chemical leading to the biomarker of interest and on potential confounders. In constructing a reference range, the sampled population is important to consider. Interindividual variability in biomonitoring results will be a function of differences not only in exposure but also in pharmacokinetics with regard to metabolic and excretory clearance. Such host factors as age, genetic polymorphisms, clinical disease, medication and alcohol use, and nutritional status can affect pharmacokinetics. The blending of those factors throughout the population generally creates a broad population distribution.

If some segments of the population are underrepresented, the full population distribution may not be adequately represented. For example, if the frequency of a metabolic genotype that slows chemical clearance occurs naturally at a rate of 30% in the population but were only sampled at a rate of 5% in the reference population, the reference range will be statistically biased low. A person in the slow-clearance group would have a biomonitoring result well above the central tendency, which would suggest high exposure. However, a reference population that is more representative of the subgroup would show that the individual result is not so different from the expected value. Developing reference ranges representative of the general population, often desirable, is sometimes difficult because sources of variability are unknown and it is impossible to try to account for key groups in their proper percentage. The hope is that the reference population will be representative if it includes large numbers of people and sampling is directed toward obvious groups (for example, of particular ethnicities, ages, and geographic areas).

Although the reference range should be inclusive and representative of the general population, it may be desirable to exclude a group from the reference population to make comparisons between the group and the reference population more meaningful. In such a case, care should be taken to describe which groups are included and which are excluded from the reference population. A reference population that excludes any particular group has the advantage of allowing comparison of that group with the remainder of the population to identify statistical differences. In the case of the slow metabolizer genotype mentioned above, keeping this group separate from the general population would allow evaluation of the impact of the genotype on biomarker levels and potentially also risk. But, including the group in the reference population allows one to determine where a particular result falls in the overall population distribution.

As another example, if biomonitoring results on people who live near a contamination source (proximity subgroup) are being evaluated, these results can be lumped in with those on the remainder of the population to create an overall distribution. However, the contribution of the group may shift the distribution, and unless there are large exposure differences (as in a bimodal distribution), it may be difficult to distinguish the proximity group from the rest of the population. Keeping the proximity group separate would allow more direct comparisons with the reference population and more relevant interpretation of study results.

Data Quality

Ideally, reference ranges are developed from biomonitoring data that conform to the study design and to data-quality considerations (see Chapter 4). For example, valid comparisons depend on comparable sampling methods for collecting data from reference and test populations. Similarly, comparisons are meaningful only if comparable statistical methods are applied in analyzing and reporting the data.

Comparison with a reference range, or with a cut point from a reference range, can be influenced by the type of data qualifiers that introduce uncertainty into any biomonitoring result. For example, short half-life is important because it detracts from how well a biomarker can represent a long-term exposure pattern. Biomarker results for a rapidly eliminated chemical are indicative only of the most recent exposure. That may skew an individual result high or low depending on the timing of sample collection relative to the last exposure. For a short-lived biomarker, the reference range would need to be developed from a large population to capture the variability contributed by sample timing in addition to the other variabilities inherent in the population (behaviors that affect exposure and pharmacokinetics).

Even with an adequate reference sample, comparison of an individual result with the reference range presents considerable uncertainty for short-lived biomarkers because of variability in a single result from a single person. Repeat sampling of a given person or other forms of exposure assessment (such as an exposure questionnaire) may be needed to improve the ability to compare an individual result with a reference range. In the case of a long-lived biomarkers, a single sampling event and a moderately sized sample population may be sufficient for useful comparisons.

It is important to note that short half-life chemicals do have the potential to be useful biomarkers for establishing the reference range if exposure is fairly frequent at about the same concentrations. In this case, rapid clearance can be balanced by frequent exposure to yield a stable blood or urinary concentration. Biomonitoring examples with cotinine and phthalates, as described in Chapter 4, illustrate this point.

Some cautions require attention. Reference ranges do not provide information on health status or risk. The primary issue is the extent to which the sampled population represents the total population. Although volumes of biomonitoring data are available from different periods and populations, the data must be reviewed to clarify the extent to which they can be used as reliable reference values for the general population and defined subpopulations. Poulsen et al. (1994) observe, for example, that most of the available data on trace elements in the Danish population are "of limited use as reliable baseline data" on that population because the studies give insufficient attention to important aspects of establishing reliable reference intervals—specifically, definition and characterization of the reference population, preanalytic factors and quality assurance of analytic methods, and statistical treatment and presentation of data. Regarding characterization of the reference population, less than half the papers reviewed by Poulsen et al. (1994) gave sufficient detail on sex, age, residence, health status, lifestyle, and occupation of the reference population. Preanalytic factors requiring attention included sample contamination during collection and instability during storage.

The ability to define a reference population can be a substantial limitation. There may be insufficient information regarding the exposure history of the reference population to a particular contaminant of interest. It is important to know the range of values of a given biomarker in a "normal" population (NRC 1991), where *normal* is regarded as without occupational exposure or without observed or hypothetical environmental exposure. However, Schulte and Talaska (1995) point out that pristine populations are rare, so "nonexposed" populations generally have some exposure of widely varied extent.

Appropriate reference populations are not always available. For example, recruiting children, especially newborns and infants, is difficult. When it is possible, the samples are usually small (European Commission 2004).

Use in the Regulatory Context

Reference-range information permits officials to compare exposures in specific geographic or demographic groups with those in the general (reference) population. The reference range may be chosen at a fixed time to facilitate evaluation of temporal trends and the effects of regulatory interventions. Because, a reference range can be critical in deciding whether public-health action is warranted (Box 5-2) or in evaluating the effectiveness of regulatory initiatives, informed attention to the construction of statistically valid and representative reference ranges is imperative (GAO 2000).

In the same vein, the absence of reliable reference ranges limits the

BOX 5-2
Reference Ranges Encourage Public-Health Action

In one community where citizens were concerned about exposure to dioxins from nearby chemical manufacturing plants, Agency for Toxic Substance and Disease Registry (ATSDR) officials had CDC's laboratory analyze blood samples and found that some residents had concentrations of several dioxins above the highest in a CDC-ATSDR-developed reference range. In response, ATSDR helped residents to obtain assistance from medical professionals expert in dioxins and, working with state and federal environmental agencies, began environmental testing to locate exposure sources (GAO 2000).

utility of biomonitoring data. Over 60% of state officials responding to a General Accounting Office (now Government Accountability Office) survey said that the lack of reference-range data prevented them from using human exposure data in their work (GAO 2000). That situation can arise when datasets are biased in some way, background exposures in the control population are not well characterized, or other sampling requirements are not fully met.

In appropriate cases, reference ranges established in other studies can provide helpful information. For example, in biomonitoring studies around hazardous-waste sites, industrial emission sources, and other point sources, it is not always possible to have a control population of sufficient size to yield an adequate reference or comparison range (Pirkle et al. 1995). As pointed out in the OP-pesticide example in Box 5-3, those types of studies often rely on a reference range developed by other investigators who worked with a broad population sample that may be unrelated to the group under investigation. If that is done, the cautions noted earlier regarding similarity

BOX 5-3
Potential Utility of Pilot Data from "Other" Populations

As part of NHANES III, a subsample of about 1,000 people provided blood and urine to determine reference ranges for 32 volatile organic compounds (blood) and 12 pesticides (urine). Demographic subgroups were defined by urban-rural status, region of the country, age, sex, race or ethnicity, and so on. The urinary measurements included metabolites of pesticides, such as carbaryl, naphthlalene, propoxur, carbofuran, parathion, and chlorpyriphos (Pirkle et al. 1995). The datasets demonstrate the feasibility of developing reference ranges for emerging analytes.

in sampling design and overall methodology between reference and subpopulation datasets are especially relevant.

As stated at the outset, reference ranges do not provide conclusions on safety or risk. Presenting that fact and other limitations is an essential aspect of communicating reference-range information to individuals, the general public, and organizational decision-makers—a topic developed more fully in Chapter 6.

ADAPTING WORKPLACE BIOLOGIC REFERENCE VALUES FOR INTERPRETING BIOMONITORING RESULTS

Comparing Occupational Reference Values with Results of the National Health and Nutrition Examination Survey

The use of reference ranges has been considered as a way to compare the exposure in an individual or group against a reference group, generally taken to mean a random sample of the general population. Another type of comparison group is workers, who represent a convenient point of reference because a number of biologic reference values have been established for this population; these values are biomonitoring criteria, typically blood or urinary concentrations, that if exceeded indicate worker overexposure to an occupational toxicant.

The frequently cited sources of biomarker reference values include ACGIH (2005), the Deutsche Forschungsgemeinschaft (DFG) (DFG 2004), and Lauwerys and Hoet (2001). In the ACGIH sourcebook on TLVs and BEIs (ACGIH 2005), BEIs were proposed for 42 substances or groups of substances (such as methemoglobin inducers). Because a number of the substances have more than one determinant (biomarker), a total of 71 determinants were reported.

Table 5-4 compares ACGIH BEIs with the NHANES median and 95th percentile for the same determinants in the July 2005 CDC report (CDC 2005). The purpose of this comparison, in conjunction with the discussions below, is to objectively assess the utility and limitations of using BEIs to interpret biomonitoring results in the general population. To make results as comparable as possible between limit values set for workers and those observed in the general population, only the distribution in subjects 20 years old and older was considered in the NHANES results. It should be noted that specifications regarding sampling time are included with the BEIs and are an integral part of the ACGIH recommendations.

As shown in Table 5-4, the NHANES median values observed for the four metals in the U.S. population correspond, on the average, to about 4% of the BEIs, whereas the 95th percentile values reach up to over 30% of the BEI. Mercury is a special case because occupational exposures to mercury

TABLE 5-4 Comparison of Biomarker Reference Values Proposed by ACGIH (2005) and Observed Concentrations in Adults for Same Determinants from NHANES 1999-2002 (CDC 2005)

Substance	Tissue	BEI	NHANES Median	% of BEI	NHANES 95th percentile	% of BEI
Cadmium	Urinary cadmium	5 μg/g of creatinine	0.27 μg/g of creatinine	5.5	0.98 μg/g of creatinine	19.6
Cadmium	Blood cadmium	5 μg/L	0.3 μg/L	6.0	1.6 μg/L	32.0
Cobalt	Urinary cobalt	15 μg/L	0.37 μg/L	2.5	1.15 μg/L	7.7
Lead	Blood lead	300 μg/L	16 μg/L	5.3	46 μg/L	15.3
Mercury[a]	Urinary mercury	35 μg/g of creatinine	0.65 μg/g of creatinine	1.9	3.0 μg/g of creatinine	8.6
Mercury	Blood mercury	15 μg/L	0.7 μg/L	4.7	4.6 μg/L	30.7
Parathion[b]	Urinary *p*-nitrophenol	0.5 mg/g of creatinine	<LOD[3]	—	0.00289 mg/g of creatinine	0.6
Pentachlorophenol	Urinary pentachlorophenol	2 mg/g of creatinine	<LOD	—	0.00206 of mg/g creatinine	0.1

[a]NHANES results for mercury are for women 16-49 years old. BEIs for mercury apply only to exposure to inorganic forms, whereas main population exposure is usually to organic forms.
[b]NHANES results are for parathion and other organophosphorous pesticides.

concern its inorganic forms almost exclusively and the BEIs apply only to these forms. In contrast, the general population is exposed largely to the organic forms. The comparisons presented in Table 5-4 are therefore of limited value for this specific metal. For parathion and pentachlorophenol, the 95th percentile values are below 1% of the BEI. PAHs are also assessed in NHANES and ACGIH proposes only one biomarker, 1-hydroxypyrene. However, ACGIH does not recommend a specific limit value for this determinant.

Comparing Biological Exposure Index and Biologischer Arbeitsstoff-Toleranz Wert

Morgan and Schaller (1999) analyzed the differences between the bases for setting Biologischer Arbeitsstoff-Toleranz Wert (BAT, Biologic Tolerance Value for Occupational Exposures) and BEI values. The BEI generally corresponds to the mean biomarker concentration that would result from inhalation-only exposure to the parent chemical at its TLV. Some workers would be expected to be able to exceed that value without harm because of inherent interindividual variability. BAT values are health-based and are conceived of as ceiling values for healthy people. As a result, BAT values are expected to be higher than BEI values. That difference underscores the importance of carefully examining the basis of a given occupational reference value before making simple arithmetic adjustments to obtain a reference value applicable to the general population.

Considerations in Deriving Reference Values for the General Population

The committee cannot make a generic recommendation on applying occupational limit values to the general population. Specifically, ACGIH explicitly states that "the values are inappropriate to use for the general population or for nonoccupational exposures" (ACGIH 2003). Similarly, DFG indicates that "BAT values are not suitable for the derivation, by means of fixed conversion factors, of biological threshold values for long-term nonoccupational exposure such as from air pollution or contaminants in food" (DFG 2004).

Thus, although it may be tempting to lower a BEI by time-weighting and uncertainty factors that extrapolate from workers to the general public, the factors listed below must be carefully considered, and such extrapolations should be used with caution. They may be appropriate in specific situations.

Route of Entry

In the occupational setting, inhalation is the main route of entry of numerous chemical substances. For some solvents (such as dimethylformamide), dermal exposure may also be a major route of entry. Ingestion usually comes last, although poor hygiene in the workplace may result in substantial exposure to aerosolized or particulate contaminants by this route. In comparison, ingestion is often the principal exposure pathway for the general population. Assuming that an objective is to protect the general population from the same systemic toxic effects as workers, the importance of potentially different routes of entry must be examined. For example, the liver first-pass effect on ingested substances might alter the proportion of metabolites formed from a parent chemical. The pharmacokinetics of a biomarker may also be modified by different rates of absorption after exposure by various routes.

Dose-Response Relationships

An occupational limit value may be set to protect workers from, for example, central nervous system (CNS) effects that might occur when exposures are near the maximal acceptable concentrations in the workplace. But CNS effects might be irrelevant for the general environmental exposure situations where a different effect might be more critical. The slopes of the dose-response relationships may be different for those various effects. In such cases, attempting to adapt the occupational limit value to environmental exposure situations by using a fixed conversion factor might be inappropriate. While evaluating the potential for the general public to develop the workplace critical effect (CNS effects may be of interest), it is important to evaluate the full toxicologic profile and determine whether other effects may present greater risks to the general public. Considerations bearing on the level of protection applied (uncertainty factors, safety factors for children, or low-dose linear approaches for carcinogens) also may differ between the occupational and the public-health setting. Additionally, when chronic exposure begins in childhood, children have many more years to live during which slowly developing adverse health effects might occur.

The workplace airborne concentration of a substance and the biomarker concentration in exposed workers typically vary as illustrated in Figure 5-5. Although such relationships aid in interpreting occupational biomonitoring data on a group basis, the effect of such variability (see Chapter 4) must be considered, as must the shape of the dose–biomarker concentration relationship at the low-dose end of the correlation. The dispersion of data points around the regression line may be due to biologic variability and partial inadequacy of air-concentration measurements for inferring actual exposure

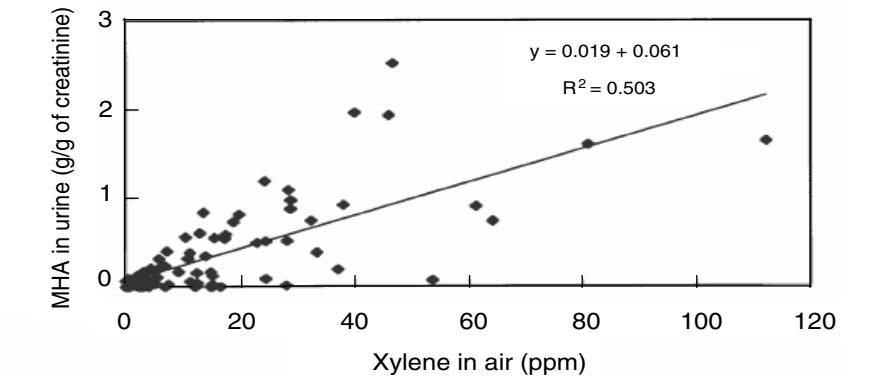

FIGURE 5-5 Daily average workplace xylene air and urinary methylhippuric acid (MHA) in exposed workers. Source: Jang et al. 2001. Reprinted with permission; copyright 2001, International Archives of Occupational and Environmental Health.

(Viau 2005). Indeed, such factors as varying ventilation rates associated with varying workloads and dermal exposure are unaccounted for by the air measurement; this might make the biomarker a better metric of the actual exposure than the air-concentration measurement of the parent chemical.

Pharmacokinetic Factors

In addition to differences in absorption pharmacokinetics—possibly due to differences in the major route of entry—physical activity, inhalation rate, and cardiac output affect absorbed and distributed doses. Greater amounts of a chemical are inhaled when respiration rate is increased, and greater cardiac output can increase chemical absorption and delivery to key excretory and metabolic organs. Those PK factors can modify the relationship between inhaled concentration and biomarker concentration, especially of metabolites detected in blood or urine. Sampling time is important. For biomarkers having a long half-life, such as urinary cadmium, sampling time is not considered critical. However, for short-lived biomarkers, such as urinary methanol, or those with a specific sampling time, such as urinary pentachlorophenol (before the last shift of the workweek), the PK rationale for setting the BEI must be considered before using this value in setting a general population reference.

Furthermore, whereas biologic limit values are set for workers exposed 8 hours/day, 5 days/week for a working lifetime, the potential exposure of the general population is generally assumed to be 24 hours/day, 7 days/week for an entire lifetime. ACGIH (2003) addresses that point as follows:

"although modified work schedules are sometimes used in various occupations, ACGIH does not recommend that any adjustment or correction factor be applied to the BEIs (i.e., the BEIs should be used as listed, regardless of the work schedule)."

Occupational exposure to chemical substances almost invariably involves multiple chemicals. That situation may result in PK interactions, which may affect the relationship between the atmospheric concentration of the parent chemical and the associated biomarker concentration (Viau 2002). For example, such an interaction is known to occur between ethylbenzene and the xylene isomers (Jang et al. 2001). Commercial xylene contains about 20% ethylbenzene, which modifies the slope of the relationship between urinary methylhippuric acid (MHA) and airborne xylene concentrations. That kind of interaction is unlikely at the subparts-per-million exposure concentrations seen in the general population. But because the BEI for MHA was obtained from the relationship observed after exposure to commercial xylene, thereby taking the interaction into account, the slope of the relationship cannot be extrapolated to the subparts-per-million range. Similar PK interactions have been observed for other mixtures but only at concentrations nearing or exceeding the occupational exposure limits (Viau 2002), so it would be a priori reasonable to consider extrapolation of the relationship between biomarker concentrations and those of their parent chemicals. For example, Tardif et al. (1991) demonstrated that, provided inhalation exposure to a mixture of toluene and xylene was kept below their airborne occupational exposure limits, there were no PK interactions between the compounds that affected the linear relationship between airborne parent-chemical exposure and urinary-metabolite concentrations. However, such an interaction was apparent at higher concentrations.

Weighing Advantages and Limitations of Using Occupational Limit Values

One of the main advantages of using occupational limit values to derive reference points for the general population is that the former apply to humans, although animal data are sometimes used in their derivation. One might therefore consider that occupational limit values alleviate the need for interspecies extrapolations. The other advantage is that the values have been used for preventing work-related diseases for years and so offer some degree of validation of the reference values.

Some of the limitations presented above can be given appropriate consideration in setting a reference value for the general population. For example, biomarkers with long half-lives are less prone to limitations in sampling time and are also probably reasonably related to cumulative exposure. In such cases, it might be tempting to apply a correction factor of 4

(rounded) to account for workweek (40-hour) vs continuous (168-hours/week) exposures and another factor that takes into account interindividual susceptibility. The workforce is usually composed of "selected, healthy" people, whereas the general population includes infants, the elderly, and the infirm. Typically, this second factor has a value of 10 in risk assessment. However, applying a total factor of 40 to the urinary cadmium BEI, for example, gives a value of 5 μg/g of creatinine ÷ 40 = 0.125 μg/g of creatinine. This would clearly be an inapplicable value for environmental exposure since it is below the median reported for the general U.S. population (CDC 2005).

The reason that time adjustment and uncertainty factors do not seem to be appropriate for extrapolation of BEIs in these cases is unclear, but it may be that internal concentrations do not scale according to Haber's law (concentration × time of exposure = a constant value) at steady state. If exposure was long enough in workplace biomarker studies to have achieved steady state (for example, at the end of the last workshift of the week), the biomarker concentration is determined more by ambient concentration rather than by time of exposure; that is, longer exposure will not achieve a higher steady-state concentration). Therefore, a simple extrapolation to the general public based on longer exposure may not be appropriate. Furthermore, although the BEIs are set to protect workers from deleterious effects of exposure to chemicals for a working lifetime, their toxicologic basis is often protection against acute effects that are not likely to be seen in the general population, whose members are exposed at much lower concentrations of the same substances and for whom long-term chronic effects are of greater concern.

Although use of BEI or an adjusted BEI to evaluate biomonitoring results in the general population is problematic, the BEI derivation may provide useful information on the relationship between biomarker and external dose. That information could be the basis of deriving a human pharmacokinetic model that relates biomarker concentration to an environmental exposure. Appendix B uses the biomarker for styrene exposure in the workplace to illustrate the limitations of BEIs with respect to the general public and to show that the data supporting the BEI can be used to construct a modeling approach that could be relevant to the general public. Styrene is a pertinent case example because the Integrated Risk Information System reference concentration (RfC) is based on the relationship between urinary biomarker and toxicity found in workers, with extrapolation back to workplace air concentration and then further extrapolation to the general public. Thus, even though the BEI itself is not directly useful for estimating risks in the general population associated with biomonitoring results, the data used to derive the BEI may become part of an RfC determination

or be used in developing a PK model. Those approaches, particularly the latter, can be useful in interpreting population biomonitoring data.

In conclusion, workplace biomarker targets (BEIs, BATs, and so on) provide a useful frame of reference for considering general-population biomonitoring results. The NHANES reports have referred to workplace biomarker targets in this manner. Comparison with workplace standards indicates whether the results found in the general population are in a range that would be of concern if found in workers. On the basis of the comparisons shown previously (Table 5-4), general-population biomarker concentrations do not typically approach workplace targets. However, for the reasons described above, it is a very inexact comparison and cannot be used to make firm judgments about the risks experienced by the general population. Furthermore, simple adjustment factors based on exposure time or sensitivity (uncertainty) factors do not appear to be appropriate for deriving biomarker concentrations for the general public. The database supporting the derivation of a BEI might be applicable to the development of human PK models that could be used to interpret biomonitoring results in the general population.

As developed in Chapter 6, workplace biomarker targets also provide context and a frame of reference for communicating general-population biomonitoring results. However, this raises a number of communication issues, given that workplace biomarker criteria are not directly relevant to the general public, for the reasons described previously and because the standards may be established with a different level of health protection than would be suitable for the general public.

USING BIOMONITORING RESULTS TO ESTIMATE RISK

Introduction

The approaches described previously can be used to relate biomonitoring results to a reference population or to workplace exposures, but they do not evaluate the risk associated with the amount of a chemical found in the body. To do that, one needs to develop a relationship between biomarker concentration and toxic response, a relationship that is not commonly derived in standard toxicologic practice. The following sections outline methods for deriving such a relationship. The approaches include the ideal case of existing risk assessments based on biomarker-response relationships established in epidemiologic research. Lead and mercury are used as examples of cases in which exposure was quantified according to hair or blood biomarkers and dose-response associations were developed on this basis.

Although applying biologic markers to risk assessment has long been

lauded as a way of reducing uncertainty (Goldstein 1996; Schulte and Waters 1999; Perera 2000; Vainio 2001; WHO 2001; Maier et al. 2004), there are relatively few such cases.

Alternatively, traditional risk assessments may help to put biomonitoring results into a risk context. Those assessments combine animal toxicology studies with human exposure assessments to estimate risks to the general population and selected groups. Biomonitoring results from those groups can then be understood on the basis of the range of risks projected in the traditional assessment. For some chemicals, exposure pathways are ill defined, and it is not possible to estimate human exposure or risk with traditional methods. In such cases, the best—perhaps only—exposure information may be the biomonitoring dataset itself. Alternative techniques, which we have termed biomonitoring-led risk-assessment approaches, will then be needed. Biomonitoring data can also inform risk assessment by identifying data gaps, replacing default assumptions, reducing exposure misclassification, or elucidating factors that affect exposure variability in a population.

Overview of Risk Assessment

Figure 5-6 outlines the classical risk-assessment paradigm along with research needs and risk management (Omenn 2003). The steps of risk assessment include hazard characterization (hazard identification and dose-response assessment), exposure assessment, and risk characterization. Risk assessment is an iterative process; conclusions derived at each step inform and refine the succeeding steps. Exposure assessment traditionally involves a pathway analysis in which chemical concentrations in various media are combined with information on human contact rates to calculate human dose in milligrams per kilogram per day. The dose is normally used in risk characterization with the reference dose (RfD), cancer slope factor, or some other estimate of potency to provide a quantitative risk estimate. Risk characterization calls for presenting the quantitative estimate with its uncertainties. The uncertainties can arise from inadequacies in toxicity data, gaps in understanding of mechanisms of action, gaps in knowledge of factors that modulate interspecies and intraspecies variability in response, or inadequacies in exposure information.

BIOMONITORING-BASED RISK ASSESSMENT

Although biomonitoring data constitute a key body of knowledge about the distribution of exposure, relatively few risk assessments have been based on biomarker-response relationships established in epidemiologic studies (WHO 2001). In a recent informal survey of leading risk-assessment prac-

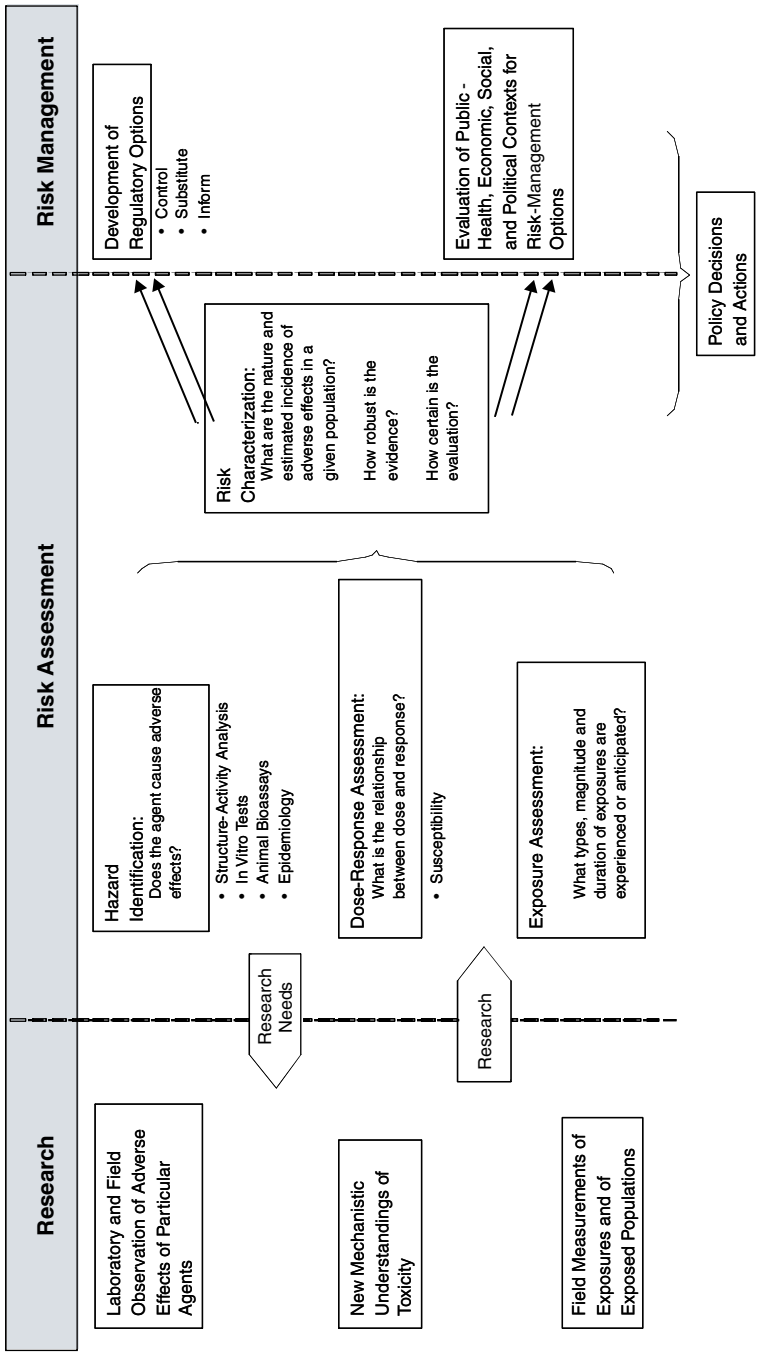

FIGURE 5-6 Evolution of risk assessment and risk management. Framework showing research, risk assessment, and risk management. Source: Omenn 2003. Reprinted with permission; copyright 2003, Human and Ecological Risk Assessment.

titioners, only a handful of cases were identified; mercury and lead were the only examples cited consistently (Maier et al. 2004). Other examples were cadmium, ethanol, arsenic, dioxin, and formaldehyde (Maier et al. 2004); of these, only cadmium and ethanol have biomarkers suitable for population screening and well-developed dose-response relationships. The best examples remain mercury and lead because of the detailed human biomarker-response information available and because of their application in public health. A sentinel feature that makes them ideal biomarkers for risk assessment is the powerful epidemiologic (prospective cohort) design that established the basis of the biomarker-response relationships. That study design is considered the pre-eminent standard in biomarker validation (WHO 2001). Pathway analyses were also reasonably complete so sources of human exposure could be identified. That was facilitated by the specificity of biomarkers of both chemicals to the exposure. The epidemiologic design and the relatively complete pathway analysis enabled the use of traditional exposure assessment involving applied dose and biomarker-based approaches in assessing risk.

Another advantage of the use of lead and mercury biomarkers is that exposure to both chemicals is more readily quantified through measurement of the biomarkers than through collection of questionnaire data or environmental measures (WHO 2001). In addition, both compounds have relatively long half-lives and therefore provide relatively stable metrics that integrate dose over long exposure periods. The lead example, which follows, details the development and utility of this blood biomarker. Similar information on mercury is presented in Appendix B.

Lead Case Study

Consistent epidemiologic and experimental data have documented deleterious effects in children associated with blood lead greater than 10 μg/dL. The data include results of eight prospective cohort studies conducted in the United States (Bellinger et al. 1992; Canfield et al. 2003; Dietrich et al. 1993; Ernhart et al. 1989), Mexico (Rothenberg et al. 2000), Australia (Baghurst et al. 1992; Cooney et al. 1989) and Yugoslavia (Wasserman et al. 1997). Effects include lowered intelligence, behavioral problems, and diminished school performance (Lanphear 2005). That body of evidence led to the identification of a blood lead concentration of 10 μg/dL or greater as the level of concern in children by both CDC and the World Health Organization (WHO) (CDC 1991; WHO 1995). The CDC and WHO determinations followed a series of reductions in the concentration of lead in blood thought to be deleterious from 60 to 40 μg/dL in 1971, to 30 μg/dL in 1978, to 25 μg/dL in 1985, and finally to 10 μg/dL in 1991 (Lanphear 2005).

However, more recent epidemiologic investigations suggest that there may not be a threshold for the adverse neurodevelopmental effects of lead in children and that the dose-response curve may in fact be steeper at blood lead concentrations less than 10 μg/dL, than at higher concentrations (Lanphear 2005; Bellinger and Needleman 2003; Canfield et al. 2003). In 2005, CDC concluded that "since no safe blood lead level in children has been identified, emphasis should be placed on efforts to control or eliminate lead in children's environment before children are exposed" (CDC 2005).

Lead is an example in which risk assessors lack an RfD for evaluating exposure doses with traditional pathway analysis. Therefore, one must use a model, the Integrated Exposure Uptake Biokinetic model (EPA 1994) for lead in children, to convert exposure doses in milligrams per kilogram per day into blood concentrations. The model takes into account numerous sources of variability and presents a population distribution of blood lead results for a given intake dose. A core feature of the model is the biokinetic slope factor, which converts exposure dose to blood concentration on the basis of empirical data on this relationship in children. The biomarker-based risk target for lead and the associated biokinetic model constitute an excellent example of the type of information and tools needed to use biomonitoring data in risk assessment maximally. This is an example of a category VII biomarker as described in the Chapter 3 categorization scheme.

The application of biologic markers to environmental epidemiology provides an optimal approach for determining whether or not biomonitoring results indicate a health risk. Chapter 7 has recommendations for leveraging of existing or planned research to assess biomarker-response relationships in a cost-effective manner within ongoing epidemiologic study designs. Many excellent reviews have been written on the specific design issues that should be considered when incorporating biologic markers into epidemiologic research (for example, Schulte and Perera 1993; Hulka 1991, Bonassi and Au 2002; Schulte and Waters 1999; Rothman et al. 1995). However, several key points illustrated by the lead and mercury case examples should be emphasized. The biomarkers must have low limits of detection. The biomarkers should be specific to the exposure of interest and reflect exposure over the hypothesized window of susceptibility. Reliable measures of the potential toxicologic end points must be a key component of the epidemiologic study design. This will require at least preliminary evaluation of potential mechanisms of toxicity from human or experimental studies or from structure activity relationships.

Comparing Biomarker-Based Risk with Population-Based Biomonitoring Results

One can compare the biomarker-based risk derived for lead with population-based biomonitoring results. Data from NHANES 2000-2001 can be used to estimate the number of children in the United States who have increased blood lead (CDC 2005). Blood lead in U.S. children declined dramatically after the removal of lead from gasoline—from a median of 15 μg/dL in 1978 to 2 μg/dL in 1999 (Rogan and Ware 2003). Nonetheless, an estimated 1.6% of U.S. children 1-5 years old had blood lead greater than 10 μg/dL in 1999-2002, according to NHANES data (CDC 2005). The major exposure sources of lead for U.S. children are deterioration of lead-based paint and the resulting dust and soil contamination (CDC 2005).

Communication issues may arise with the use of biomarker-toxicity relationships, in part because of the high level of confidence that investigators place in the results. Researchers may be tempted to extrapolate from a biomarker concentration to a health effect in an individual or group. For example, biomonitoring data have been used to extrapolate to the number of pregnant women in the general population who may beat increased risk from methyl mercury exposure (NRC 2000). As described in Chapter 6, risk communication for such extrapolations needs to capture the uncertainties in the numerical estimates (number of people with increased mercury concentrations), and the health significance of surpassing a particular "bright line" biomarker concentration.

USING EXISTING RISK ASSESSMENTS FOR INTERPRETING BIOMONITORING DATA

Interpretation of biomonitoring results can be enhanced by existing risk assessments of a specific chemical. Traditional risk assessment calculates the dose associated with various exposure pathways, cumulates the pathways into a total dose, and then compares the total dose with the RfD or uses it to estimate cancer risk. A comprehensive exposure and risk assessment for the general population, if available, can be a useful starting point for interpreting biomonitoring data. For example, if the risk assessment indicates that the general public, including high-end individuals, is exposed on average to levels less than the RfD, then biomonitoring results showing widespread population exposure may still not raise a health concern. Alternatively, if the risk assessment indicates that a typical exposure can increase risk, then biomonitoring data that show widespread exposure may lead to health concerns for the general population, especially for those in the upper percentiles of exposure. Ideally, the risk assessment will provide an analysis

of scenarios that involve high-end exposures and susceptible populations (such as young children) to point out whether particular groups are important to include in biomonitoring studies.

Appendix B provides brief case studies of two pesticides, glyphosate and permethrin, for which a pre-existing risk assessment can help to put biomonitoring results into perspective. In both cases, the Environmental Protection Agency (EPA) has evaluated risks for a wide array of exposure scenarios as part of the reregistration process, and there are biomonitoring data whose interpretation could benefit from these risk assessments.

BIOMONITORING-LED RISK-ASSESSMENT APPROACHES

Biomonitoring-led risk assessment is needed when the biomonitoring and toxicology databases are robust but epidemiologic data are not adequate to establish the biomarker-response relationship and there are few exposure data. In such cases, biomonitoring results may raise important health questions that cannot be answered without knowing more about exposure. There are three main options for converting biomonitoring data into a format that can be used as exposure information in risk assessments:

- Use human PK modeling (Box 5-4) to convert the biomonitoring data into a human-exposure dose that can be related to an RfD, cancer potency value, or other toxicity value.
- Use animal PK modeling to convert the dose-response relationship seen in toxicity studies (applied dose) to a dose-response relationship based on internal dose, using a dose metric derived from human biomonitoring data. This approach fosters the development of a biomarker-response relationship and biomarker-based toxicity values.
- Collect sufficient biomarker data in animals to express the dose-response relationship in key toxicology studies in terms of a biomarker-response relationship, in addition to an applied dose-response relationship.

Using Biomarker-Led Approaches to Assess Risks Associated with Biomonitoring Results

Option 1: Conversion of Biomonitoring Data to Exposure Dose with Human Pharmacokinetic Modeling

In the sections below, four different cases for converting biomonitoring data to exposure dose using pharmacokinetic modeling are considered: lipid-soluble, bioaccumulative chemicals at steady state; lipid-soluble, bioaccumulative chemicals not at steady state; shorter-half-life chemicals at

BOX 5-4
Brief Overview of Pharmacokinetic Models
(See Appendix C for Expanded Discussion)

PK modeling can take the form of relatively simple models that treat the body as one or two compartments. The compartments have no precise physiologic meaning but provide sites into which a chemical can be distributed and from which a chemical can be excreted. Transport rates into (absorption and redistribution) and out of (excretion) these compartments can simulate the buildup of chemical concentration, achievement of a steady state (uptake and elimination rates are balanced), and washout of a chemical from tissues. The one- and two-compartment models typically use first-order linear rate constants for chemical disposition. That means that such processes as absorption, hepatic metabolism, and renal excretion are assumed to be directly related to chemical concentration without the possibility of saturation. Such models constitute the classical approach to PK analysis of therapeutic drugs (Dvorchik and Vesell 1976) and have also been used in selected cases for environmental chemicals (such as hydrazine, dioxins and methyl mercury) (Stern 1997; Lorber and Phillips 2002). As described below, these models can be used to relate biomonitoring results to exposure dose under some circumstances.

Physiologically based pharmacokinetic (PBPK) models have been seen as an advance in that they describe physiologically relevant compartments into which a chemical is taken up and eliminated on the basis of blood flow, partitioning properties, and clearance mechanisms. PBPK models have the advantage of being able to simulate chemical concentration in specific target tissues, such as brain, fetus, and thyroid (Rao and Brown 1993; Thrall et al. 2002; Gentry et al. 2003); nonlinear kinetics, such as metabolic saturation; protein and macromolecule binding; route-specific differences in chemical disposition; formation of primary and secondary metabolites and their concentrations in specific tissues; blood flow limitations of metabolism and clearance (Kedderis and Lipscomb 2001); intake routes and exposure scenarios; population variability through the interface with probabilistic Monte Carlo techniques; and interactions with chemical mixtures.

PBPK models rely on a series of simultaneous differential equations that simulate chemical delivery to tissues via the arterial circulation and removal via the venous circulation. The models are run in time steps such that the entire course of chemical disposition can be presented for calculation of the area-under-the-curve (AUC) dose, often a key metric for chronic risk assessment. The physiologic parameters can be adapted for different species, sexes, age groups, and genetic variants to facilitate extrapolation from one type of receptor to another.

The classical compartmental and more complex PBPK models require actual pharmacokinetic data to calibrate some parameters such as metabolic rate constants. However, PBPK models are more data-intensive and require greater numbers of chemical-specific and receptor-specific inputs. Although PBPK models have been used extensively in the last 20 years to address cross-species differences and other uncertainties, there are cases in which simpler one- or two-compartment models have been sufficient for risk assessment, for example for methyl mercury (EPA 2001).

pseudosteady state; and short-half-life chemicals that do not approach steady state.

Human Modeling Case 1: Lipid-Soluble, Bioaccumulative Chemicals at Steady State

The extensive body-burden work done with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and its congeners (Lorber and Phillips 2002; EPA 2003) has provided a model for converting biomonitoring data into dose estimates. Although some aspects pertain specifically to highly lipid-soluble, bioaccumulative chemicals, there are elements that may be suitable to other chemicals. Figure 5-7 shows the general framework for a one-compartment model for interpreting biomonitoring serum data for lipid-soluble chemicals under the assumption of steady state.

The construction of this type of model and the requisite calculations are illustrated in Appendix B on the basis of the work done with TCDD. A one-compartment model can yield estimates of intake dose that can be used in risk assessment, but it should be considered a screening-level analysis that is applicable to long-term average exposure. More complete physiologic models that take into account not only lipid partitioning but also protein binding, the induction of metabolizing enzymes, blood flows to lipid and other compartments, and non-steady-state kinetics (for example, due to changes in intake dose) are advances that should be used to simulate shorter-term fluctuations in biomarker concentration (Emond et al. 2005a,b).

Human Modeling Case 2: Lipid-Soluble, Bioaccumulative Chemicals Not at Steady State

Even though chemicals with long half-lives and high storage in lipid tend to have stable concentrations, they may not be at steady state. For example, dioxin body burdens apparently increased in the early part of the 20th century and then declined over the last 2 decades. That pattern repre-

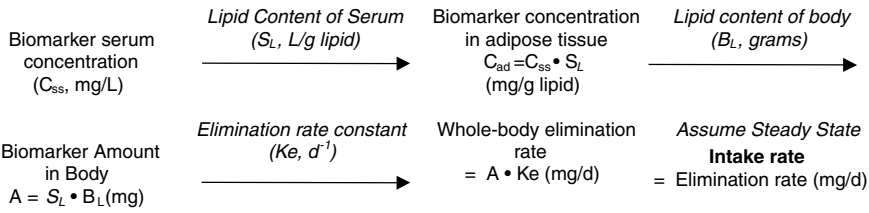

FIGURE 5-7 Conversion of biomonitoring data to daily dose on the basis of one-compartment (body-burden) model.

sents a nonuniform exposure and thus a non-steady-state condition. It can still be addressed with simple one-compartment modeling as described above, but the exposure dose is varied to match the temporal trends in the biomonitoring data (Pinsky and Lorber 1998). The dose profile that best matches the biomonitoring data can then be used for risk assessment.

Human Modeling Case 3: Shorter-Half-Life Chemicals at Pseudosteady State

Chemicals that are not highly lipid-soluble and that have relatively short half-lives (hours to days) do not build up a stable long-term reservoir. However, a pseudosteady state can be attained if exposure is nearly uniform and constant (Figure 5-8). Pseudosteady state refers to the case in which blood or tissue concentrations are changing and therefore are not completely stable. These blood or tissue concentrations fluctuate slightly and in a regular pattern around the average concentration.

If that is the case, blood concentrations may be relatively stable, and there is a potential to convert biomonitoring results into exposure estimates in a manner analogous to that described above for TCDD. The difference is that starting from a blood or serum concentration, one needs the volume of distribution (Vd) to estimate the total amount in the body. The general framework is as shown in Figure 5-9.

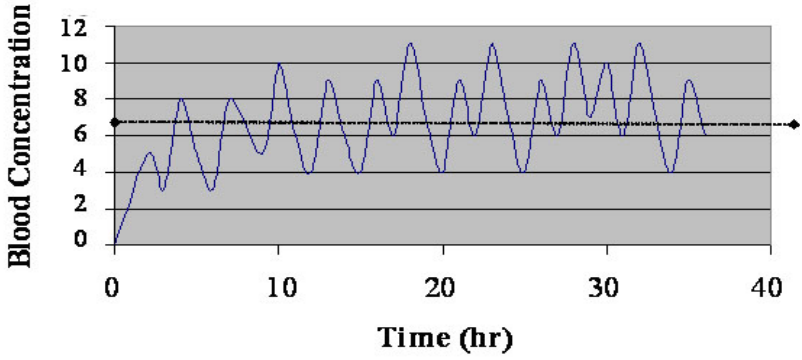

FIGURE 5-8 Blood concentrations of rapidly cleared chemical to which there is frequent and nearly uniform exposure. Highlighted line (♦—♦) is mean blood concentration. Under these exposure conditions, biomarker concentration will be within a factor of 2 of mean after first several hours. Simplifying assumption of pseudosteady state (mean concentration is approximated by concentration found at any sampling time) may suffice for estimating exposure dose from blood concentration under these circumstances.

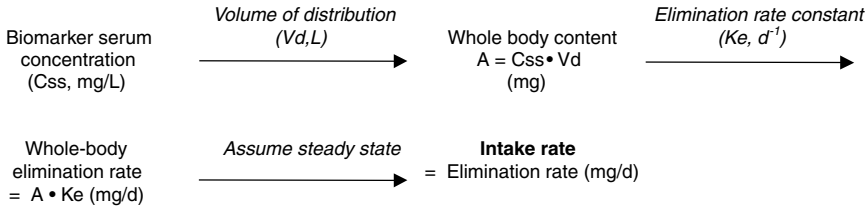

FIGURE 5-9 Conversion of biomonitoring data to daily dose on basis of one-compartment model for non-lipid-soluble chemicals at steady state.

Vd is a characteristic of the chemical that depends on its water and lipid solubility, protein-binding properties, and affinity for storage depots, such as bone. It is largely independent of dose unless transport and storage mechanisms are saturable. In general, the more water-soluble or plasma-protein-bound the chemical, the smaller will be its Vd. (The more lipid-soluble, the higher the Vd.) Chemicals that bind extensively to receptors in tissues may have a larger Vd than expected simply on the basis of partitioning principles. The Vd of a chemical can be determined experimentally in animals and extrapolated to humans or derived from physicochemical properties (lipid solubility and protein-binding capacity). For a one-compartment model the Vd is simply the adminstered dose divided by the initial plasma concentration.

Derivation of Vd relies on the ratio of dose and blood concentration immediately after intravenous administration. Two-compartment models involve more complex calculations to estimate Vd at steady state that reflect the transport of chemical between compartments as well as out of the body.

In summary, conversion of biomonitoring data to exposure dose requires knowledge of chemical elimination rate and Vd and requires that conditions be approximately pseudosteady state. It may be useful to estimate dose from body burden; however, this cannot be used to interpret an individual's biomonitoring result, because the elimination rate and Vd would not be known. Reasonable bounds on elimination rate and Vd could be used to calculate an upper end of daily dose that is still compatible with the biomonitoring results (for example, when both Vd and elimination rate are high).

Methylmercury is a primary example of this type of model in humans. A human mercury one-compartment PK model has been developed on the basis of several exposure datasets in which blood or hair concentrations have been measured at various times after methyl mercury exposure (Stern 1997; Kershaw et al. 1980; Sherlock et al. 1984). The one-compartment model takes into account the elimination half-life of mercury from blood and methylmercury volume distribution (in blood) to back-calculate the

exposure dose needed to achieve a mercury concentration in blood. That is the basis of the methyl mercury RfD (EPA 2001). Although it is intended primarily for use under steady-state conditions, the model is predictive of non-steady-state conditions and in fact was used to assess the single fish-meal mercury intake needed to exceed the blood concentration associated with the RfD (Ginsberg and Toal 2000). That example and the one described above for TCDD demonstrate the potential utility of simple one-compartment models in interpreting biomonitoring data and in converting blood or tissue concentrations to applied doses in humans.

Case Example: Pharmacokinetic Calculations to Interpret Phthalate Urinary Biomarker Data. The previous descriptions focused on blood or adipose biomarker concentrations that were converted to body burden to yield estimates of daily dose based on chemical half-life. A modified form of that is conversion of urinary biomarker data to daily exposure dose via simple model calculations as described for phthalates.

The biomonitoring of phthalates in urine has been of increasing interest as methods to detect the metabolites of specific phthalates have improved in recent years. Human exposure to phthalates comes from food via leaching from plastic packaging, from personal-care products, from children's toys, and from medical procedures that involve the storage of fluids in plastic bags or their delivery via flexible tubing (Hauser and Calafat 2005). The CDC dataset on samples collected in 2001-2002 (CDC 2005) included analysis of 12 phthalate metabolites reflecting exposure to eight phthalates, including the most commonly used phthalates: diethylhexylphthalate (DEHP), diethylphthalate, two forms of dibutylphthalate, butylbenzylphthalate, di-*iso*-nonylphthalate and di-*n*-octylphthalate. The samples were collected from a subsample of the total NHANES population (N = 2,780) and constituted a followup of rounds of phthalate-metabolite collection involving about 2,500 subjects in 1999 and 289 subjects in 1988-1994 (Blount et al. 2000; Silva et al. 2004). A much smaller sampling of phthalate metabolites in nonoccupationally exposed German subjects (N = 85) has been reported (Koch et al. 2003).

The widespread detection of phthalate metabolites in human urine has produced questions about public-health risks, especially with regard to antiandrogen effects that can influence male gonadal development (Gray et al. 2000; Parks et al. 2000). The extrapolation from urinary biomonitoring results to exposure and risk assessment has been facilitated by calculations that convert urinary metabolite concentrations to intake dose of the parent phthalate (Koo et al. 2002; Koch et al. 2003; Kohn et al. 2000; David 2000). The parent diester phthalates are rapidly and completely metabolized to the monoester metabolites, which are rapidly cleared by the kidney. Those features allow one to assume that the daily excretion rate of metabolite is equal to the daily intake rate of the parent chemical. Furthermore,

because phthalates are ubiquitous and exposure occurs daily, one can assume pseudosteady-state conditions. Preliminary evidence that that is the case has been presented in several human studies (Hauser et al. 2004; Hoppin et al. 2002).

Biomonitoring data have been converted to daily exposure dose (e.g., Koch et al. 2003) by calculating the amount of metabolite excreted per day (amount in urine per gram of creatinine times creatinine excretion per day); adjusting for the fractional excretion of metabolite (some of the phthalate metabolites account for as little as 1 or 2% of total chemical excreted, whereas others account for 70%); and adjusting for the difference in molecular weight between metabolite and parent chemical. That approach was used to convert urinary biomonitoring data from the NHANES 1988-1994 dataset to the daily intake rate (in micrograms per kilogram per day) for seven phthalates (Kohn et al. 2000). Confidence in the resulting exposure estimates was provided by comparison with the results of exposure analyses conducted on the general population with traditional pathway analysis, taking into account the major sources of exposure (phthalates in food and indoor air) and minor sources (CERHR 2000; Kohn et al. 2000). Table 5-5 shows the estimated exposures of the general population (Kohn et al. 2000).

Table 5-5 shows that the biomonitoring-based exposure estimate for DEHP had a median of 0.71, a 95th percentile value of 3.6, and a maxi-

TABLE 5-5 Estimated Exposures (μg/kg/day) to the General Population Based on Extrapolated Intake from Urinary Metabolites in 289 Individuals Measured by Blount et al. (2000)

Monoester	Diester	Minimum	Median	95th percentile	Maximum	CERHR[a]
Ethyl	Diethyl	<LOD	12	110	320	NA
n-Butyl	Di-*n*-butyl	0.084	1.5	7.2	110	2- 10[b]
Benzyl	*n*-Butyl benzyl	0.094	0.88	4.0	29	2[c]
Cydohexyl	Dicyclohexyl	<LOD	0.026	0.25	2.3	NA
2-Ethylhexyl	Di(2-ethylhexyl)	<LOD	0.71	3.6	46	3- 30
n-Octyl	Di-*n*-octyl	<LOD	0.0096	0.96	13	<3- <30[d]
i-Nonyl	Di-*i*-nonyl	<LOD	<LOD	1.7	22	<3- <30[d]

[a]The CERHR Phthalates Expert Panel held its third and final meeting 12-13 July 2000 in Arlington, Virginia; the CERHR final reports on the seven phthalates evaluated along with a full description of the center and its activities are available on the CERHR Web site.
[b]The upper bound for occupational exposure was estimated as 286 μg/kg/day: the estimate of 2 μg/kg/day is at the 84th percentile of our calculated values.
[c]The CERHR estimate for *n*-butyl benzyl phthalate is at the 11th percentile of our calculated values.
[d]Di-*n*-octyl and di-*i*-nonyl phthalate estimates from the CERHR were reported as less than for di(2-ethylhexyl) phthalate.
Source: Adapted from Kohn et al. 2000.

mum of 46 μg/kg per day (N = 289). The exposure-pathway analysis yielded a range of 3-30 μg/kg/d, demonstrating reasonable concordance, given the vast difference in approaches. A similar degree of concordance between biomonitoring-based and exposure-pathway-based estimates of phthalate daily doses was reported by David (2000).

There are several interesting features of the phthalate biomarker-exposure dose analyses. First, women and children have greater exposure to several phthalates than male adults. That may be due to the use of cosmetics and personal-care products in the case of women and due to higher food intake rate per body weight and exposure to plasticizers in toys in children. Data on children younger than 6 years old are not available, and this may be an important data gap. The other feature of note is that the relatively small German study found exposures to some phthalates that were 3-20 times above those found in the United States, whereas for other phthalates the exposure differential was smaller and concentrations in the United States were greater (Koch et al. 2003). That implies a different exposure pattern in different countries.

The risk associated with phthalate biomarker results has not been formally analyzed. However, exposure doses estimated from the German biomonitoring data suggest a potential concern about DEHP in that the range of dose estimates was 2-185 μg/kg per day, whereas the EPA RfD is 20 μg/kg per day and the tolerable daily intake of the European Commission Scientific Committee on Toxicity, Ecotoxicity and the Environment is 37 μg/kg per day (Koch et al. 2003). The lower exposure doses estimated in the Kohn et al. analysis suggest that most people in the United States are below the RfD for DEHP. However, caution is needed regarding this risk conclusion, in part because the RfD was established in 1991 on the basis of increased liver weight in rodents after DEHP exposure (EPA 1991). More recent research indicates that reproductive effects, particularly structural and functional changes in the testes, constitute an important toxicologic end point (Kavlock et al. 2002). Furthermore, testing of effects during the late gestational and neonatal periods, thought to be times of particularly high sensitivity, is incomplete (Kavlock et al. 2002). A recent epidemiologic study of male postnatal measures in relation to maternal prenatal urinary concentrations of four phthalate metabolites suggests that biomarker results within the reference range are associated with altered male reproductive development (Swan et al. 2005). Although results from that study should be considered preliminary, in part because of the small sample and the use of a novel index (anogenital distance) to assess reproductive development, they highlight the need for additional epidemiologic research in light of the widespread phthalate exposures (Kaiser 2005). Future research involving biomarker-response relationships for phthalate metabolites may obviate the extrapolation of biomarker results to exposure dose followed

by comparison with the traditional RfD. Nevertheless, the case study demonstrates the utility of estimating exposure dose from urinary biomarker data for potential application to risk assessment.

The phthalate example illustrates the utility of a Group VI biomarker as described in the Chapter 3 framework. Phthalate urinary metabolites are reliable biomarkers of parent-chemical exposure, there is sufficient information to extrapolate exposure dose from biomarker concentrations (assuming that near steady-state conditions apply), and exposure dose-toxicity relationships in animals are available. If biomarker-toxicity relationships are more firmly established in humans (as in a followup to the Swan et al. 2005 study), it might be possible to recategorize phthalate metabolites as Group VII biomarkers.

One caveat in basing exposure dose on urinary-biomarker data is that the percentage conversion of the parent chemical to the biomonitored metabolite needs to be well established and not highly variable. For example, for some of the phthalates, the biomarker accounts for a very small percentage of total chemical fate; numerous other pathways account for the remainder. That necessitates a large numerical adjustment in going from the urinary measurement to the exposure-dose estimate—an adjustment that is subject to interindividual variability in the percentage disposition via the measured biomarker. In fact, there is some disagreement as to the fraction of DEHP excreted as the urinary biomarker; the conflicting estimates ranging from 2.4% to 13% (Koch et al. 2004). Each urinary-metabolite result in the population actually represents a range of exposure doses governed by the degree of intersubject variability in the fraction of biomarker excreted. A probabilistic analysis of the phthalate urinary dataset may be appropriate for displaying the full range of exposure-dose estimates.

Another important caveat has to do with how the urinary concentration of a biomarker is expressed. If it is expressed simply per volume of urine, then the estimate of daily biomarker output can be misinterpreted because urine volume is variable from day to day and over the course of a day. Biomonitoring results from spot urine samples can be greatly influenced by changes in the water content of urine when expressed on a volume basis. To correct for that, urinary biomonitoring results are often also expressed as per gram of creatinine (CDC 2005) on the assumption that the creatinine-excretion rate is less variable than the water-excretion rate. In the phthalate example described above, the creatinine adjustment is used not only to express the biomarker result but also to convert it to a milligrams-per-kilogram-per-day dose by multiplying by the grams of creatinine excreted per day. That is a convenient way to derive an estimate of exposure, but it carries the uncertainty that creatinine-excretion rate can also be a substantial source of variability (Barr et al. 2005). For example, analysis of NHANES III data on 3,400 men (20-29 years old) found a 6-

fold spread in urinary creatinine concentrations across the 10th to 90th percentiles of this population. The distributions in boys 6-11 years old and elderly men (for example, over 70 years old) were shifted to the left in such a way that the means were about 60% of the means for men 20-29 years old. Other important age, sex, and race or ethnicity differences in urinary creatinine concentrations were also evident (Barr et al. 2005). The differences in total amount of creatinine excretion per day would be somewhat larger than that described above for creatinine concentration because the groups with low creatinine (children and the elderly) also have less urine output per day. Thus, creatinine-excretion rate is a substantial source of variability in calculations that convert a urinary biomarker concentration to a dose of parent chemical. One could simulate that variability and its influence on estimates of intake dose with Monte Carlo modeling techniques.

The chlorpyrifos example described in Appendix B illustrates another caveat related to biomarkers that are urinary metabolites. A metabolite can sometimes appear in urine not only as a result of parent-chemical uptake and metabolism but also as a result of uptake of the metabolite from environmental media (Lu et al. 2005; Wilson et al. 2003). Thus, the biomarker for chlorpyrifos, 3,5,6-trichloro-2-pyridinol (TCP), occurs in a wide variety of environmental media, and the concentration in foods surpasses that of the parent chemical (Morgan et al. 2005). If the intake of the metabolite from environmental sources is substantial in comparison with that of the parent chemical, as in the case of chlorpyrifos and TCP, the extrapolation of urinary biomarker concentration to parent-chemical exposure dose is uncertain.

Human Modeling Case 4: Short-Half-Life Chemicals That Do Not Approach Steady State

The last case is that of chemicals that are not highly lipid-soluble or long-lived and are unlikely to be at steady state. Population biomonitoring data, however, may be able to present a reasonable distribution of internal concentration if the sample size is sufficient. A one-compartment model may be used, with knowledge of elimination rate and Vd, to estimate exposure dose of the average person. As above, there is uncertainty with respect to how variability in elimination rate and Vd may interact to affect dosimetry. There is also uncertainty in sample timing, inasmuch as the sample may have been taken at any point along the elimination phase of the most recent exposure. Those factors preclude a definitive calculation of daily dose, but approaches described in Appendix B for chlorpyrifos and trichloroethylene (TCE) can yield screening-level estimates that are useful in initial risk assessments for biomonitored concentrations of these chemicals. The chlorpyrifos example illustrates the use of urinary-metabolite data

to estimate intake dose, which when augmented with human activity and exposure models can simulate exposure patterns that could have produced the biomonitoring result. The chlorpyrifos biomarker, TCP, is available for intake in environmental media, so not all of what is measured in urine comes from the metabolism of the parent chemical.

Studies which involved controlled human exposure to volatile organic compounds (VOCs) combined with repeated blood sampling have enabled researchers to evaluate the utility of PBPK models for interpreting biomonitoring results taken under non-steady-state conditions (Canuel et al. 2000; Tan et al. 2005; Sohn et al. 2004).

The TCE example demonstrates the utility of Bayesian inference techniques and bounding approaches for estimating the relationship between blood concentration and exposure pattern. Additional illustrations involving toluene and chloroform have shown the potential utility of PBPK modeling approaches for VOC biomonitoring data (Canuel et al. 2000; Tan et al. 2005). In the case of toluene, a PBPK model run in reverse was able to use exposure time and biomonitoring results as inputs to accurately predict the ambient exposure concentration (Canuel et al. 2000). With population-based biomonitoring, the exposure time relative to the sampling time is not known. Therefore, Tan et al. (2005) used Monte Carlo uncertainty analysis together with PBPK modeling to evaluate a range of potential exposure scenarios (for example, water concentration and timing of exposure) resulting from chloroform blood levels found in tap water exposure studies.

Option 2: Use of Animal Pharmacokinetic Modeling to Derive Biomarker-Based Dose-Response Relationship

Human biomonitoring data can be interpreted through animal biomarker-response relationships in a manner parallel to that with which human exposure information is interpreted through applied dose-response relationships. The latter relationship is typically used to derive an RfD or a cancer potency value that can be expressed as risk. A number of steps are used to convert the animal dose-response relationship to an RfD or cancer slope factor that is expressed in units of applied dose (mg/kg/d) and thus is not directly relevant for interpreting the internal exposure data obtained in biomonitoring studies. However, a number of steps can be used to convert the animal dose-response relationship in applied dose units to the corresponding RFD or cancer slope factor in units of internal dose (biomarker). The same steps used in setting an RFD (application of uncertainty factors and extrapolation to low dose) would be used in deriving the biomarker-

based toxicity value, which would be of direct use in interpreting risks associated with biomonitoring results.

The biomarker-response relationship may be constructed through PBPK modeling as described in this section or through direct measurements of biomarker concentrations in animals as described in the next section.

One issue in deriving biomarker-based toxicity values is that the typical exposure-response relationship is in the form of total daily dose vs toxic effect. The applied dose metric, although crude, integrates exposure over 24 hours. However, a biomarker measurement at a single time often is not a time-integrated dose but merely an isolated data point. The ideal is to express the internal concentration as an integrated internal dose, also called the area under the concentration-time curve (AUC). That can be accomplished by simulating chemical fate over 24 hours (or longer) and estimating the AUC for each dose that was used in the toxicology studies. The AUC-response relationships can then be used to derive the biomarker-based equivalent of an RfD or cancer potency value.

For long-half-life chemicals, the internal concentration can generally be considered stable and the human concentration measured at a single time can be multiplied by 24 to estimate the 24-hour AUC (EPA 2005).[2] That approach can also be used for shorter-half-life chemicals if exposure can be assumed to be relatively uniform and continuous, so that the biomonitored concentration reflects the long-term average internal concentration. If those conditions do not apply, it may not be possible to estimate human AUC from a single biomonitoring result. In such a case, the animal biomarker-response relationship may need to be based on a single point on the internal-concentration-response curve. If one picks the lowest concentration (for example, at the end of the time course after much washout has occurred), most of the exposure will be missed. If one picks the peak internal concentration, the blood concentrations required to produce an effect will be higher, and the risk assessment will be less conservative than otherwise. Picking the lowest or highest internal concentration is an arbitrary decision, so it may be most practical to pick the average concentration achieved over 24 hours as a reasonable correlate to the toxic effects. In that case, the biomonitoring concentrationss would be assumed also to represent an average for that day of exposure and thus could be compared directly with the animal biomarker-based dose-response relationship. Although that involves an assumed course in human blood, it can provide a reasonable first approximation of the blood concentrations and of its significance with respect to biomarker-based toxicity values.

[2]The committee is aware that EPA 2005 and EPA 2003, cited later in this chapter, are in draft form; they are cited here simply for illustrative purposes.

Pharmacokinetic Modeling in Animals: PFOA Case Example

Biomonitoring data on perfluorooctanoic acid (PFOA) has led to questions of exposure and risk, and efforts to address these questions have involved pharmacokinetic modeling in animals. A draft risk assessment of PFOA evaluates the potential risks associated with concentrations found in human serum (EPA 2005). The main form of exposure assessment in the analysis is biomonitoring data on the U.S. general population. PFOA biomonitoring datasets involve serum samples from blood-bank specimens from adults (N = 645), from a prospective study of an elderly population (N = 238; age, 65-96 years), and from a clinical trial in children (N = 598; age, 2-12 years). The data yielded geometric means of 4-5 μg/L for all three age groups, but regression analysis of the children's data showed that age was inversely related to serum PFOA concentration (Olsen et al. 2004). The risk assessment used a margin-of-exposure (MOE) approach in which serum concentrations associated with no-observed-adverse-effect level (NOAELs) or lowest observed-adverse-effect levels (LOAELs) in animal toxicology studies were divided by the geometric mean or 90th percentile of biomonitoring serum results. The animal serum concentrations were derived with two methods: for toxicity end points in monkeys, serum PFOA measurements were available throughout the toxicity studies, and the steady-state concentration associated with the LOAEL was used in MOE calculations; and for toxicity end points in rats, a PK model was used to estimate serum concentrations at LOAEL or NOAEL doses. The PK model runs were informed by limited plasma data on rats; these data were used to calibrate the model and extrapolate across individual points to develop AUC estimates. A one-compartment PK model was selected for predicting serum concentrations by using linear (first-order) rate constants to describe chemical absorption and elimination. The backfit elimination rate constants reflected the large sex-dependent difference in clearance; the female elimination rate was 37 times greater than that of the male.

Figure 5-10 provides evidence that the PFOA model developed by EPA is predictive when tested against male rat plasma PFOA data from 90-day dietary studies. The data represent steady-state PFOA concentrations. Figure 5-10 also shows that the model was successful in simulating the limited data available for non-steady-state conditions for plasma concentrations in pregnant rats. Those validation runs suggest that the model is suitable for estimating LOAEL and NOAEL internal doses across a range of PFOA toxicity end points in rats (subchronic, chronic, reproductive, and developmental). The internal LOAELs and NOAELs could then be used for comparison with biomarker data on humans.[3]

[3]It was not possible to construct PK models of the dosimetry in nursing pups, because of difficulties in estimating pup dose via lactation related to the likelihood of more rapid clear-

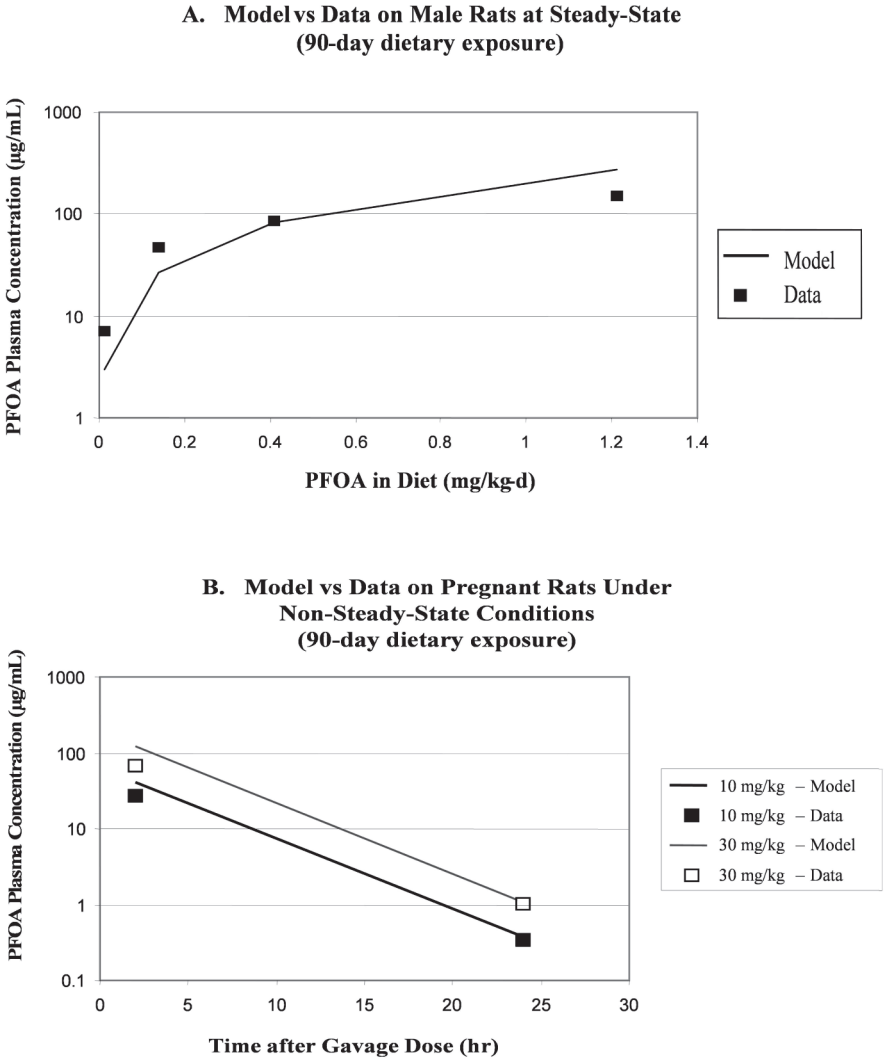

FIGURE 5-10 Predictiveness of PFOA rat model. Source: Data from EPA 2005, Appendix 1.

The PK models predicted both peak and AUC serum doses for the rat toxicicity end points. The human biomonitoring data are more likely to

ance in these younger animals (Han 2003). Therefore, estimates of serum concentrations in lactating pups were not constructed, and MOEs for toxicity end points for this life stage could not be calculated.

represent a steady state rather than a peak, so the AUC rat data were more relevant for comparison with human exposure. In addition, PFOA toxic effects may be more likely to be related to the cumulative internal dose than to peaks. The biomonitoring data were converted from the single data point to AUC by multiplying the PFOA concentration by 24 to reflect the expectation that the measured concentration would be constant over the entire day. That is a safe assumption, given the long half-life of PFOA in humans (about 4 years). Those modeling predictions and calculations allowed for a direct comparison between rat and human AUC, which resulted in the MOE analysis.

The PFOA risk assessment showed that the MOE for several toxicity end points was 1,000-fold or higher but was somewhat smaller in the adult female rat NOAEL (200- to 400-fold). The MOEs for end points relevant to children (such as, maturation of juvenile rats) were large, around 10,000-fold. However, as stated above, it was not possible to model rat lactational AUCs; furthermore, the human biomonitoring age group does not include lactating children. Given that PFOA is excreted into breast milk and that there was an inverse correlation between age and serum PFOA in the human dataset, measurement or modeling of nursing infants may be an important addition to the risk assessment.

Another uncertainty in the children's MOE analysis is that the biomonitoring data showed that perfluorooctanoates related to PFOA—perfluorohexansulfonate and N-methyl perfluorooctanesulfonamidoacetate—were considerably higher in children than in adults. The reason is unknown, but the original authors suggest that it may reflect a different exposure pattern in children (Olsen et al. 2004). Toxicology and exposure data on these analytes are not sufficient to enable a separate risk assessment to evaluate the children's exposures.

A final consideration is that there is a large PK difference between rats and humans with respect to half-life: in rats, it is hours (in the female) to days (in the male), whereas in humans, it is about 4 years (EPA 2005). The steady-state AUC modeling approach used in the MOE analyses takes half-life in rats into account and is independent of human half-life because of the likelihood that the biomonitoring data represent steady-state concentrations. However, the large cross-species half-life difference raises the possibility of other PK and pharmacodynamic cross-species differences that are not adequately captured in the MOE analysis.

In summary, the PFOA risk assessment is a good example of biomonitoring-led risk assessment. There is no attempt to calculate exposure dose with pathway analysis, because the sources of human PFOA exposure are too uncertain. Instead, the biomonitoring data served as the sole source of human exposure information. Those data could be interpreted in a risk-assessment framework with the aid of PK mod-

eling of rat dosimetry in key toxicology studies and with the aid of limited biomarker measurements in monkey and rat studies. Thus, although an RfD is not available for PFOA, these types of animal-human biomarker comparisons are useful to put the degree of human exposure into a risk context. Uncertainties exist in the PFOA analysis with respect to cross-species extrapolation of PK and toxicologic results, other perfluoro biomarkers in humans have not been tested in animals (the aggregate-risk question), and key PFOA toxicity end points could not be fully compared with the human biomonitoring data (because of limitations in early-life analyses). Those uncertainties are indicative of what one can expect to encounter when conducting similar biomonitoring-led analyses.

Option 3: Obtaining Sufficient Animal Pharmacokinetic Data to Develop a Biomarker-Response Relationship

In Option 3, the biomarker-response relationship would be developed from actual measurements rather than (or in addition to) PK models. The biomarker-toxicity relationship would be quantified directly from results of the experimental bioassay by investing additional effort in gathering biomarker data (such as, blood and urinary concentrations) at doses relevant to key toxicology studies. A parallelogram approach similar to that derived from the work in the 1970s by Sobels (1977) could be used to extrapolate experimental biomarker results in animals to human health risk assessment as is now commonly done with exposure dose-response relationships (Sobels 1977; WHO 2001; Perera 1986; Sutter 1995). Adding biomarker measurements to 90-day and 2-year bioassay designs may not require substantial cost but may be instrumental in interpreting human biomonitoring data in the future. Because biomarker measurements are not part of standard animal toxicology protocols, there are relatively few examples of this approach. Even after toxicity studies are completed, it is possible to recreate the conditions of such animal tests and obtain biomarker information useful for relating biomarker concentration to toxicity.

The approach for collecting biomarker data on animals that is relevant to human risk should initially involve animal PK studies to determine possible sampling media (blood, plasma, and urine) and biomarkers (such as, parent chemical, metabolites, and hemoglobin adducts). Consideration should be given to the toxic mechanism and to half-life. The former is important in selecting the most relevant biomarkers. The latter is important in making the biomarker reliable for screening human populations even under conditions of sporadic exposure. If biomonitoring data on humans

already exist, the human biomarker should be applied to the animal PK testing to the greatest extent possible.

Once a suitable biomarker is selected, the biomarker-toxicity relationship can be generated through biomarker-data collection during toxicology studies, possibly requiring a satellite group of animals to generate the biomarker data. If the critical dose-response studies have already been conducted, one can recreate the design (species, dose route, and dose) for a limited number of animals to generate biomarker data that could be related to the previous toxicity findings. Alternatively, it may be possible to construct a PBPK model based on the PK data already collected that could simulate the key toxicology studies and generate a biomarker-toxicity relationship. Chemical-specific partition coefficients would also be needed to develop the model (Gargas et al. 1989). The World Health Organization has outlined ways in which biomarker data can assist in such modeling efforts (WHO 2001).

In a number of cases, PK data have been collected as part of toxicity testing in animals. For example, the National Toxicology Program (NTP) has added PK studies to its test battery of short-term, long-term, and genotoxicity studies (Buchanan et al. 1997). That information is used to evaluate the potential for nonlinearities in the dose-response relationship due to such phenomena as metabolic saturation. It is helpful in selecting doses for NTP's chronic bioassays, learning about a chemical's mechanism of action, and interpreting the results of toxicity studies. The PK studies are not designed specifically for the interpretation of human biomonitoring data, but that may be possible in a post hoc fashion. It may require PBPK modeling in which a model would be constructed for the species used for toxicity testing, and it would be calibrated to the PK data developed as part of the animal testing. The calibrated model could then be used to convert the dose-response relationship found in toxicity studies to an internal dose (biomarker-response) relationship, and the latter could be extrapolated to humans to interpret biomonitoring data. In the PFOA example described, biomarker measurements in animals were used to help to interpret human biomonitoring data. Although there are few examples of this type of approach, it should become more applicable if biomarker measurements are routinely incorporated into experimental bioassays.

As in other risk-assessment approaches (e.g., NRC 1994), scientific uncertainties are a predictable feature of any new biomonitoring-led risk assessments. As shown above and discussed more fully in Chapter 6, identifying and communicating those uncertainties—such as the effect of interindividual variation in elimination rate and limits on extrapolating adult PK data to children—are critical in communicating the risk results.

Hemoglobin Adducts as Biomarkers of Exposure

This chapter has focused on the interpretation of biomarkers of exposure, specifically biomarkers circulating in blood or excreted in urine or breast milk. Hemoglobin adducts are an additional type of exposure biomarker. They are unlike the more traditional biomarkers in that they represent *integrated* exposure, the cumulative dose of an agent that can irreversibly bind to hemoglobin. They depend not only on the intensity of exposure but also on the length of exposure, the reaction rate with hemoglobin, and the lifespan of red blood cells. Methods have been developed for converting hemoglobin-adduct concentrations to daily exposure to acrylamide and ethylene oxide (Calleman 1996; Tornqvist and Landin 1995). That approach is useful for chemicals that form reactive metabolites that would otherwise be too transient to measure in bodily fluids. Thus, it is one step closer to the biologically effective dose and so is a potentially important type of biomarker in risk assessments of reactive chemicals (Tornqvist and Ehrenberg 2001).

One hemoglobin adduct, carboxyhemoglobin, is a special case in that it is both an indicator of exposure and an effect. Carboxyhemoglobin is the key biochemical derangement caused by carbon monoxide, so its concentration is directly related to health risk. For other biomarkers that utilize hemoglobin adducts, hemoglobin is not the biochemical target.

Other types of internal adducts (DNA and RNA adducts) are further in the direction of biomarkers of effect and pose interpretive challenges in addition to the challenges that spring from exposure and PK factors. For example, rates of DNA repair can differ widely between tissues and types of adducts, so its use as a biomarker of exposure or effect is more complex.

Interpretation of BM in Terms of Exposure Assessment

Chapter 5 has provided an overview of approaches to assess the biomonitoring-response relationship. However, exposure assessment is also a critical component of risk assessment, since if risks are determined to be excessive, pathway analyses must be carried out to identify the major sources of exposure. This includes not only the immediate sources such as house dust, water, food, indoor air, or soil, but also the initial sources from which human exposure pathways originate (for example, industrial emissions, transportation sources, or consumer products). While dose reconstruction can be difficult, the NHEXAS approach referenced in Chapter 2 should be more broadly applied (Pang et al. 2002). This involves obtaining detailed environmental sampling and survey information at the same time that biomonitoring samples are collected. Such data-intensive biomonitoring efforts may not be feasible for large numbers of subjects but can be conducted on a representative subset

of the population of interest. Exposure pathways found to be key contributors to internal dose can then be explored to determine the initial steps of contaminant entry into the environment.

It may be possible to use Geographic Information Systems (GIS) to map biomonitoring results to determine whether there is a spatial pattern in exposure concentrations. This could be overlaid with GIS maps of environmental data (for example, air or water pollution or distribution of waste sites) to determine whether biomonitoring results correspond to specific environmental sources. However, mapping techniques are generally not useful for sporadic, localized sources such as food or consumer products. In such cases, survey questionnaires and sampling of the home environment are of more direct use in understanding exposure sources.

Chapter 7 presents the committee's recommendations on approaches that should be utilized to obtain data on exposure-biomarker relationships within ongoing large-scale biomonitoring studies.

Utility of Biomonitoring Data to Inform Risk Assessments

Biomonitoring can facilitate risk assessments in many ways. These are discussed below.

- It demonstrates that exposure of the general population or specific groups is occurring. Classical exposure pathway analyses are hypothetical constructs with many assumptions about human behaviors that lead to exposure. The finding of a chemical in blood or urine documents that exposure has occurred and may indicate whether exposure is widespread or occurs only in isolated cases.
- It demonstrates the range of exposures, the degree of interindividual variability, and the potential for highly exposed subpopulations. Classical pathway assessments are typically limited in their analysis of variability, perhaps estimating dose for a central tendency and an upper-bound case. Application of probabilistic Monte Carlo techniques can provide a hypothetical population distribution of exposure doses. However, the distribution depends on robust input of human metrics and behaviors (such as soil ingestion rates), which may not be available. The tails of such distributions can be particularly uncertain. Biomonitoring data on a broad, representative sample can provide a distribution of internal doses that can improve on Monte Carlo estimates of variability and have the potential to identify subpopulations that may be more exposed. That information can be used in risk assessment to estimate exposures and risks at upper tails of the distribution. It may also enable future assessments to focus on the subpopulations identified. Such future assessments might include pharmacogenetic probes to determine whether biomarker concentrations are high because of

high intake or because of metabolic traits that lead to enhanced retention. Given that young children are often more highly exposed to environmental chemicals than adults (EPA 2000), it is important to include them in biomonitoring studies.

- It can establish population exposure baseline values and status and trends. Risk assessment may lead to risk-management decisions to intervene and thus decrease exposure. Biomonitoring data can document the baseline exposure and how it is affected by risk-management interventions in multiyear status and trends biomonitoring programs. Biomonitoring studies have demonstrated the success of public-health and regulatory programs in decreasing exposure to lead, environmental tobacco smoke (with serum cotinine biomonitoring) (CDC 2005), and chlorpyrifos (Whyatt et al. 2003; Whyatt et al. 2005).
- It can identify chemicals and risk-assessment questions for which there are key research gaps. Biomonitoring data on widespread human exposure raise questions about risk and indicate where data gaps exist. Addressing the gaps will be instrumental in developing a risk assessment. A case in point is polybrominated diphenyl ethers (PBDEs). Biomonitoring studies of PBDEs in breast milk found an increasing trend that correlated with societal use of flame retardants in consumer products during the 1980s and 1990s (Birnbaum and Staskal 2004). Figure 5-11 shows that PBDE concentrations in breast milk in North America exceed those found in Europe, with a steep rise in the Canadian (and presumably also U.S.) concentrations in the last decade (Schecter et al. 2003). However, there is still little understanding of the exposure sources and pathways that have led to the biomonitoring results. Furthermore, the toxicology database is only in the initial stages of development; key end points (such as, hormonal and neurodevelopmental effects) need further exploration (Birnbaum and Staskal 2004). The rising trend in PBDE bomonitoring results and their implications for exposure of nursing infants have led to a major research focus on exposure sources, toxic effects, and health risks.
- It can estimate exposure via breast milk. Biomonitoring of breast milk provides information directly applicable to assessing infant exposure and risk from nursing. The measured breast-milk concentration is the starting point for exposure calculations that include breast-milk intake rate per unit body weight. The nursing dose estimates can then be used to assess risks during the postnatal period on the basis of toxicity end points developed from developmental studies or from adults and extrapolated to the postnatal period. Exposures via breast milk may be especially important for persistent organic pollutants that bioaccumulate in fat, because they are efficiently transferred through the milk to the breastfeeding infant (Landrigan et al. 2002). Examples include DDT, polychlorinated biphenyls, and PBDEs. However, water-soluble nonpersistent chemicals may also par-

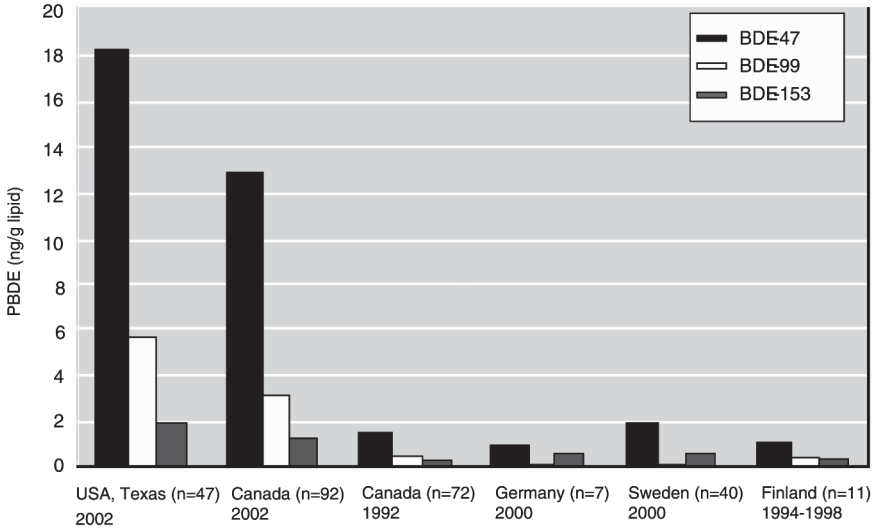

FIGURE 5-11 Median concentrations (ng/g lipid) of BDE-47, BDE-99, and BDE-153 in human milk from different countries. Data from Ryan et al. (2002) and Ryan and Patry (2001) for Canada, from Schroeter-Kermani et al. (2000) for Germany, from Noren and Merionyte (2000) for Sweden, and from Strandman et al. (2000) for Finland. Source: Schecter et al. 2003.

tition to some degree into the water fraction of breast milk. Models that predict the degree to which a chemical will partition into breast milk (Fisher et al. 1997) can be used to help to determine which contaminants should be the focus of breast-milk biomonitoring studies.

- It can assess in utero exposure. Any substance in the maternal circulation can be transferred across the placenta to the developing fetus unless it is first metabolized and eliminated (Ginsberg et al. 2004). Risk assessment of the fetal period typically relies on maternal dose. However, biomonitoring of cord blood relative to maternal blood may be important to document whether there are substantial maternal-fetal differences in exposure. Evidence on methylmercury suggests that it concentrates in the fetus (Stern and Smith 2003), whereas an evaluation of 29 pesticides suggests similar concentrations across the maternal-fetal unit (Whyatt et al. 2003).
- It can assess risks posed by multiple exposures. Large-scale biomonitoring studies illustrate the need for developing cumulative risk-assessment approaches for biomonitoring data because exposures are typically to mixtures rather than to single toxicants. An examination of the *Third National Report on Human Exposure to Environmental Chemicals*, for example,

gives some indication of the extent of mixed exposures in the United States. Concentrations of 148 chemicals or chemical isomers in 12 broad chemical classes were measured in blood or urinary samples collected from a representative sample of the U.S. population; biomarker concentrations at the 50th, 75th, 90th, and 95th percentiles of the population distribution were presented (CDC 2005). In almost all cases, multiple compounds in each chemical class were detected in at least half the urinary or blood samples collected. For example, all but two of the 13 metals measured in urine were detected in at least 50% of samples. Similarly, when nine phthalates were assessed in urinary samples in the 2001-2002 NHANES (the first year in which phthalates were measured), metabolites of six were detected in 50% or more of samples: dimethyl phthalate, diethyl phthalate, dibutyl phthalate, butylbenzyl phthalate, di-2-ethylhexyl phthalate, and di-*n*-octyl phthalate. Metabolites of multiple organophosphorous insecticides were also detected in 50% or more of samples. Although mixed exposures to compounds in the other chemical classes did not appear to be as extensive, biomarkers of one or more chemical in each class were found in at least 50% of the samples. Given the current paucity of data on approaches for assessing risks associated with biomarker mixtures, research into risk-assessment techniques for these types of mixtures should be used (see Chapter 7). Several recent small-scale epidemiologic studies have evaluated risks associated with combinations of biomarkers and can provide illustrations of various potential approaches (see for example, Swan et al. 2005; Whyatt et al. 2004; Castorina et al. 2003). In addition, multiple contaminant exposures can be addressed by designing animal bioassays in which the animal exposures mimic a human environmental exposure pattern. (Examples of such mixture bioassays are discussed in Chapter 7.) The mixture bioassays in animals, with PBPK modeling approaches (also discussed in Chapter 7), may address some of the multiple-contaminant issues that are presented by population-based biomonitoring data.

The committee recommends that CDC's *National Reports on Exposure to Environmental Chemicals* present population distributions showing the number of chemicals (and chemical classes) detected per person. For both mixtures and single chemicals, the committee recommends that the data in the national exposure reports be presented for the full range of the distribution (including the 10th and 25th percentiles of the distribution), rather than just at the 50th percentile and above.

SUMMARY

Biomonitoring data often provide an indication of human internal exposure to environmental contaminants, and this becomes the springboard

for important public-health or clinical questions. As defined at the outset of this chapter, these questions are

- Is the biomonitoring result in a range that is typical of the general population?
- Does the biomonitoring result indicate a health risk?

The answer to the first question can be obtained with descriptive statistics and straightforward comparisons between the individual result and the reference range. That assumes that sufficient data are available to define a reference range and that it has been properly constructed for the general population. The answer to the second question is more complex and requires information from diverse sources, including toxicology, epidemiology, exposure studies, pharmacokinetics, and risk assessment. Those are all well-established fields, but only recently have they developed a focus on the interpretation of biomonitoring data. Therefore, there are a number of data gaps, uncertainties, and other limitations in developing risk assessments that can explain biomonitoring results. Risk communication needs to recognize those limitations in developing messages about the meaning of chemical concentrations in human blood, urine, or other media.

This chapter has provided a variety of options for interpreting biomonitoring data, all of which have utility for specific situations and applications. There are wide differences in the amount of information available on different chemicals and biomarkers, so the approach to answering the second question will vary between chemicals. A useful way to summarize the different approaches is with the case studies provided throughout the chapter and in Appendix B. Case-study chemicals were selected because they provide the type of information needed for interpreting biomonitoring data and thus are useful to illustrate the options discussed in this chapter. However, data on many chemicals that are evaluated in biomonitoring studies are not available; this represents a data gap that hinders the interpretation of biomonitoring data on most of the chemicals currently sampled.

Summary of Case Studies: Exemplifying the Interpretation of Biomonitoring Data

The case studies presented in this chapter and in Appendix B exemplify a variety of interpretive options. Table 5-6 and the associated text summarize the case-study biomarkers in terms of their utility, supporting data, and the interpretive option that they exemplify.

Uncertainties and Limitations in Interpreting Biomonitoring Data

Throughout this chapter, in connection with each of the several approaches to interpreting biomonitoring data, points of confidence (strengths) and limitations or uncertainties (weaknesses) have been identified. For example, such studies as NHANES are strengths, providing a nationally representative survey and a wealth of data on a large number and variety of biomarkers. The lead and mercury case studies demonstrate a strength, showing that biomonitoring data can be interpreted directly from powerful epidemiology datasets in which the collection of biomarker data was central to the study. The PFOA case is important to show that the increased use of animal PBPK modeling can be a strength for the interpretation of biomonitoring results. The increasing availability of PK data and analyses points to new possibilities for using biomarker data in the risk-assessment process.

As in classical risk assessment, there are numerous uncertainties in interpreting biomonitoring data: cross-species extrapolations, interindividual variability, extrapolation from external to internal dose, high-dose-to-low-dose extrapolations, and the effect of mixtures as opposed to single chemicals. How those uncertainties would affect interpretation of a particular biomonitoring result depends on the question being asked and the robustness of the biomarker's database. Key uncertainties in the realm of reference range include the potential to misrepresent the general population because of undersampling of some groups and oversampling of others and the potential to misclassify an important group as part of the general population. Increased attention to enrollment criteria in population biomonitoring studies and potential future uses of genetic markers indicative of metabolic capability can help to inform these kinds of uncertainty.

The risk interpretation of biomonitoring results will tend to have additional uncertainties. That is because, in addition to the standard uncertainties encountered in risk assessment, there is the uncertainty of extrapolating from a blood or urinary concentration to an external dose. There will be variability both in the timing between sample draw and most recent exposure and in the relationship between blood concentration and dose. Those kinds of variability are compounded by uncertainty in the ability of a PK calculation or model to convert biomarker to dose accurately. For example, reliance on urinary biomarker results expressed per gram of urinary creatinine leads to an uncertain calculation of total chemical excretion per day because of the considerable variability in creatinine clearance per day. That complicates an otherwise simple approach to estimating dose. Furthermore, the conversion requires knowledge of fractional excretion via various pathways, which may not be present for a large sample of humans. The uncertainties created by these factors can be bounded via sensitivity and Monte

TABLE 5-6 Properties of Biomarkers Used as Examples in Chapter 5

Chemical	Biomarker	Type of Information Available	Possible Applications
Glyphosate	Urinary glyphosate	Exposure pathways risk assessment; external dose to toxic effect in animals; limited analysis of biomarker to external dose	Biomarker results can be put into risk context by using existing risk assessment
Permethrin	Urinary carboxylic acid metabolites	Exposure pathways risk assessment; external dose to toxic effect in animals	Biomarker results can be put into risk context by using existing risk assessment
PBDE	PBDE congeners in blood and breast milk	Emerging exposure and toxicity database	Biomarker results useful for demonstrating need for research and establishing reference range
PFOA	Serum PFOA	External dose to toxic effect in animals; biomarker to animal external dose; therefore, biomarker to toxic effect in animals	Biomarker results can estimate human risk; need to extrapolate biomarker-response relationship across species
Lead	Blood lead	Biomarker to toxic effect in humans; biomarker to external dose in humans	Biomarker results can be used directly for estimation of human risk; exposure apportionment and intervention possible
Mercury	Blood mercury	Biomarker to toxic effect in humans, although this relationship is for cord blood; biomarker to external dose in humans	Biomarker results can be used directly for estimation of human risk; exposure apportionment and intervention possible
Chlorpyrifos	Urinary TCP	Biomarker to external dose in humans; external dose to toxic effect in animals; therefore, biomarker to toxic effect in animals	Biomarker results can estimate human risk; need to extrapolate external dose-toxicity relationship across species

Dioxin	Dioxin in blood or lipid	Biomarker to body burden and external dose in humans; body burden and external dose to toxicity in animals	Biomarker results can estimate human risk; exposure intervention possible
Styrene	Urinary metabolites	Biomarker to external dose (air concentration) in workers; external dose to toxicity in animals biomarker to toxicity in workers	Biomarker results can estimate risk in workers but not directly applicable to general population.
TCE	Blood TCE	External dose to toxic effect in animals; biomarker to animal external dose; biomarker to external dose in humans	Biomarker too transient to be a reliable index of exposure of general population.
Phthalates	Urinary monoester metabolites	Biomarker to external dose in humans; external dose to toxic effect in animals; therefore, biomarker to toxic effect in animals; preliminary biomarker to effects in humans	Biomarker results can estimate human risk; need to extrapolate external dose-toxicity relationship across species

Carlo analysis, but ultimately the variability in fractional excretion and creatinine clearance needs to be understood to characterize population exposure to urinary biomarkers.

A major factor governing variability in biomonitoring results is interindividual differences in metabolic clearance. Genetic polymorphisms can affect the activity or inducibility of Phase I and Phase II metabolic enzymes, potentially affecting both the activation and detoxification of xenobiotics (Perera 2000; Eaton 2000). Biomonitoring results for parent compounds in blood or metabolites in urine or blood will be influenced by these differences. This can be a large factor if the enzyme systems involved are highly variable across the population. For example, a polymorphism in the CYP2D6 gene has a large influence on the clearance of certain drugs, CYP2E1 is inducible by exposure to alcohol, and glutathione conjugation to epoxides can be affected by null polymorphisms in several glutathione transferases (Thier et al. 2003; Ingelman-Sundberg 2005; Kessova and Cederbaum 2003). The design of biomonitoring studies should include an evaluation of the dominant clearance pathways for the chemical being monitored. If these pathways are modulated by genetic polymorphisms, then genotype probes should be considered when collecting the biomonitoring samples. This would be consistent with the increasing use of genotyping methods in environmental epidemiology studies (Nebert et al. 1996). This can decrease uncertainty and assist in data interpretation, pointing out whether a high biomonitoring result may have been from high intake or slow clearance. These can have very different risk implications.

Another kind of uncertainty is related to the utility of occupational reference values for comparisons with general population biomonitoring results. The workplace targets are inappropriate for a general population that includes infants, the elderly, and the infirm.

The committee's attention to those limitations and uncertainties is important for two reasons. First, full disclosure of limiting factors gives scientists and the public a fuller understanding of the reliability and credibility of biomonitoring results. It provides risk assessors with information needed to "characterize" risk conclusions fully, as called for by the National Research Council risk-assessment paradigm (NRC 1983; 1994). Second, and equally important, the kinds of uncertainty define data gaps for immediate attention and related long-term research needs.

CONCLUSIONS

This chapter identifies a variety of approaches for interpreting biomonitoring results, ranging from descriptive to risk-based. The descriptive approaches are useful as a first step in analyzing biomonitoring data, but they do not describe the level of risk. That requires the risk-based approaches

described in the chapter. Although the methods presented are feasible, minimum data are required to exercise the various interpretive options. These minimal data are lacking in the case of numerous chemicals, so priorities need to be set in selecting biomarkers for expansion of the database to enable assessment of risk.

The committee drew the following conclusions about descriptive approaches:

- Descriptive approaches are important in laying a foundation that risk-based approaches can build from, and in some cases they are the only type of analysis needed.
- The reference-range approach is a critical data layer that summarizes the biomonitoring dataset and enables comparisons between segments of the population and times. Although they do not provide information about risk, simple comparisons between an individual's biomarker concentration and the population distribution may be all that is needed to answer key questions about the need for personal action.
- Workplace biologic exposure targets (such as BEIs) provide another point of reference that may be of some use in assessing the relative degree of individual or group exposure outside the workplace.

Risk-based approaches try to determine how much risk is associated with a given biomarker result. Those approaches and their interpretive power vary widely with the extent of information available on a chemical and its biomarker.

The committee drew the following conclusions about risk-based approaches:

- The biomarkers of greatest utility for interpreting risk are those for which biomarker-toxicity relationships have been developed in humans, as in the case of lead and mercury.
- If such relationships are not available, biomonitoring data may be interpreted by converting them to human exposure dose with the aid of PK models. That can be done in different ways depending on the chemical and the type of biomarker (for example, parent chemical and metabolite).
- For persistent lipid-soluble compounds, conversion of blood or adipose tissue biomonitoring results to body burden and intake dose is feasible even with simple one-compartment models, although multicompartment physiologic models can provide a more flexible and improved tool for estimating dose.
- Approaches for less lipid-soluble and nonpersistent chemicals can depend on whether a blood or urinary biomarker is available.

- Urinary biomarkers can be related to exposure dose in a straightforward manner for chemicals that are excreted rapidly in urine. This approach requires the collection of data describing the percentage of dose excreted each day in urine and percentages excreted by different metabolic and elimination pathways. There can be important variability and uncertainty in those factors and in the normalization of the biomarker result (per gram of creatinine). Furthermore, there may be environmental sources of the urinary biomarker that can confound an estimation of parent-chemical dose based on the metabolite in urine. It is also possible that the urinary metabolites may exist as breakdown products in the environment.
- An alternative interpretive approach is to leave the human biomonitoring result as is but develop applied dose-biomarker relationships in animals. That requires obtaining animal PK data to support PBPK modeling or the collection of animal biomarker information in study designs that mimic key toxicology datasets.

RECOMMENDATIONS

Improved interpretation of biomonitoring results will require the expansion of the database typically available on many chemicals. The following recommendations will help in the evaluation of exposure and risk associated with biomonitoring results in general. More specific recommendations can be made case by case after an individual chemical's database is reviewed.

- Increase the use of biomarkers in environmental epidemiology studies.
- Develop biomarkers suitable for determining internal dose-response or excreted dose-response relationships in animal studies with confirmation of biomarker applicability to humans.
- Improve animal toxicology study designs to incorporate use of validated biomarkers to characterize biomarker-response relationships that can be used to interpret human biomonitoring data.
- Expand use of exposure assessment in the biomonitoring study protocol to identify exposure sources and allow a pathway-exposure analysis that could help to interpret biomonitoring data.
- Research is needed on various aspects of chemicals mixtures beginning with better reporting from population-based biomonitoring studies on the number and diversity of chemicals found in subjects. New bioassays are needed that explore the health outcomes of environmentally relevant mixtures (that is chemicals and amounts found in human tissues). PBPK models also need to be expanded to better understand chemical-chemical interactions.

- Research the factors governing human excretion of chemicals in urine and breast milk and how it can affect biomarker results:
  - —How breast-milk content changes over the course of the lactational period can affect excretion of toxicants into breast milk.
  - —How uncertainties and variability in creatinine clearance can affect urinary biomarker results and their extrapolation to external dose.
- Identify to what extent exposures to chemical degradation products in the environment contribute to metabolite levels measured in urine samples, as certain urinary metabolites may exist as breakdown products in the environment.
- Add a wider variety of media to biomonitoring studies, especially media that will provide information about early life stages. For example, biomonitoring of breast milk can inform about exposures during infancy, and biomarkers in cord blood and meconium can inform about fetal exposure.
- Include in utero exposures and young children in biomonitoring designs because they are a substantial source of population variability in exposure and susceptibility.
- Improve human dosimetry models to simulate life stages and population groups (for example, those with polymorphisms) that have not been biomonitored; this may allow extension of biomonitoring results to vulnerable groups that are difficult to identify or sample.
- Incorporate metabolic-trait determination into biomonitoring studies (for example, genotyping or phenotyping of metabolic traits) to understand how the traits can affect biomonitoring results.
- Expand modeling approaches and case examples in which nonsteady-state biomonitoring data are simulated to explore the exposure conditions responsible for biomonitoring results; this may provide exposure estimates that can be used in risk assessment (for example, Bayesian inference techniques and population behavior-exposure models).
- Increase research emphasis on the low and high ends of the biomarker distribution to discover what leads to these tails and thus enhance the development of exposure interventions if warranted.

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6

Communicating Results, Interpretations, and Uses of Biomonitoring Data to Nonscientists

Very recent history has seen tensions aroused by monitoring of human tissues to assess exposure to environmental chemicals and the consequent importance of communication about biomonitoring. For example, concern over whether biomarker data would prompt new mothers to abandon beneficial breast-feeding for fear of contaminating their children helped to scuttle proposed biomonitoring legislation in California. Biomonitoring makes environmental exposure personal (Chapter 1), raising concerns about materials that seem out of place in the human body, such as perchlorate in breast milk and flame retardants in fetal cord blood. However, there is also great anxiety over "erroneous" use of biomonitoring data to reach premature conclusions about health effects or contaminant sources and exposure reduction. Another example of communication issues within "fractious debates" (Chapter 4) concerned the Centers for Disease Control and Prevention (CDC) release of its 2005 report on biomonitoring data. Two allegedly competing implications were trumpeted by outside groups: "The nation is awash in toxics." "Look at the progress made in reducing exposures." Anxiety among laypeople can be heightened by frequent reporting of biomonitoring data that are not fully explainable with current scientific knowledge.

Communication is essential for proper interpretation and use of biomonitoring data. Earlier in this report, we emphasized the intricate and mutual involvement of analysis, management, and communication of environmental biomonitoring (Chapter 1); the contentious social and political context with diverse constituencies for biomonitoring information; and the need to incorporate communication-evaluation planning, consideration of

partnerships, and constituency assessment into study design (Chapter 4). This chapter focuses on issues entailed in reporting results of biomonitoring studies and in discussing their interpretation and use. If study design included partnership with one or more constituencies, continued partnership on implementation of evaluation and of reporting results is prudent. Partnerships could be undertaken even without prior partnership in the study planning, but evaluation is likely to determine that communication would have been even more effective if partnership had begun earlier. Constituency assessment should have been completed by the time results are reported, although a significant lag time since the planning stage might necessitate updating this assessment to ensure there have been no critical changes before communication of results begins. Public perceptions about uncertainty, exposure, and other biomonitoring-relevant topics discussed in this chapter might inform constituency assessment as described in Chapter 4. The remainder of Chapter 6 assumes that appropriate evaluation planning and implementation, partnership consideration and implementation, and constituency assessment have been done, and therefore this chapter focuses on reporting of results, interpretation, and use.

Without effective communication in particular between biomonitoring researchers and nonscientists and among nonscientists, proper interpretation and use of biomonitoring data will occur only with difficulty, conflict, anxiety, and waste of time and money. The challenges for biomonitoring reflect those common to communication of risk assessment (not to mention risk management) as identified by the field of risk communication. There are failures by information generators to characterize interpretation of data fully and fairly, or to attend to constituent information needs or concerns; failure of information reporters to fully convey information complexities, and caveats while avoiding simple "sound bites"; and by information recipients to be prepared (for example, with knowledge and attention) to deliberate adequately on the information's meaning for risk management.

Because the literature on biomonitoring-specific communication is extremely scarce, this chapter addresses risk communication issues most relevant to biomonitoring.

LIMITS OF THIS CHAPTER'S DISCUSSION

First, we focus here on communication with nonscientists, partly because that is where the challenges often are the most difficult[1] and partly

[1]Communication among scientists (such as toxicologists, epidemiologists, and risk assessors) about biomonitoring can be fraught with problems. However, the focus of this chapter is on the communication path between scientists and nonscientists, where the nature of the problems and potential solutions is less understood.

because that is where the sketchy evidence on communication issues is centered. We also see scientists, as well as institutional policy-makers and communicators, as among the prime audiences for this chapter's advice on communication. As noted in Chapter 4, potential discussants of environmental biomonitoring are more diverse than just "laypeople" and "experts," and there is great diversity within each constituency cited in Chapter 4 in the nature and degree of beliefs relevant to biomonitoring. Communication is best described as at least a two-way, if not a multiple-voice all-talking-at-once, conversation in which scientists are not the sole generators of biomonitoring data (see Chapter 2), let alone the only ones able to interpret and use the data.

Second, the committee does not equate nonscientists with the general public, although much of the current scientific literature on lay beliefs and attitudes relevant to biomonitoring focuses on the latter. We treat nonscientists as a broader category because that describes reality: even in universities, some biomonitoring communicators and constituents are laypeople, and that is the case even more in government agencies, business firms, foundations, activist groups, and amongst politicians, as well as "the general public."[2] The need to distinguish biomonitoring communication for informing citizens from that for informing other constituencies is unclear.[3] No doubt, similarities can be taken too far such as in giving an organization a clinical consultation, or assuming that officials of an agency or firm are unreceptive to quantitative data or explicit consideration of tradeoffs between variously uncertain health benefits and similarly uncertain exposure-reduction costs. The literature on reporting scientific results to lay decision-makers in government and other institutions (e.g., Brown 1985; NRC 1989; Balch and Sutton 1995; Stern and Fineberg 1996; Andrews 1998; PCCRARM 1997; Thompson and Bloom 2000) can be useful. Potential diversity is the reason to support research on how biomonitoring-related concepts might differ among discussants. How-

[2]Scientists also occur in all these groups, including politicians, activists, and the general public; presuming that a constituency's members have no relevant expert knowledge or scientific sensibility can be a serious mistake.

[3]For example, Brown (1985) on "presenting risk management information to policymakers," PCCRARM (1997) on "risk assessment and risk management in regulatory decision-making," and Thompson and Bloom (2000) on "communication of risk assessment information to risk managers" include topics and recommendations familiar to readers of guides on risk communication to the public. They discuss, for example, the need to consider the larger context (for example, What makes this decision important? What do various stakeholders think about it?); challenges of conveying uncertainty accurately and effectively, whether it entails qualitative or quantitative measures; how risk comparisons can be helpful or misleading; and risk differences among management options. Thompson and Bloom (2000) go so far as to suggest "using risk managers as representatives of the public to assess the effectiveness of different communication methods."

ever, until such research is conducted, it would not be incorrect to treat biomonitoring knowledge of, and communication with, nonscientists as if there are no differences within that group other than those that a competent and early constituency assessment (Chapter 4) would take into account in determining how to design an effective biomonitoring study. We do not minimize the challenges of communicating to different constituencies, but we believe that at this stage of the art, far more is to be gained by stressing similarities among biomonitoring communication of all types.

Third, the scientific literature on risk perception and communication reviewed in the rest of this chapter is based entirely on external-exposure monitoring and other nonbiomonitoring aspects of environmental issues. To the committee's knowledge, no studies have directly explored biomonitoring beliefs or communication. We assume that the cited literature can be extrapolated to biomonitoring, but without evidence that it is a safe assumption. The risk communication literature shows that generalization from experience or other research topics can backfire if not verified with empirical testing (for example, Morgan and Lave 1990). That is why the communication-research agenda recommended by the committee is critical: it will fill a serious gap in our knowledge that has been left by the nonbiomonitoring priorities of researchers and research funders—and a gap probably not fillable without explicit funding by biomonitoring sponsors.

Fourth, although good communication is critical for interpretation and use of biomonitoring data, this dictum should not blind anyone to the limits of what communication about biomonitoring can accomplish, given the volatile social and political context cited in the introduction to Chapter 4. Communication will not eliminate all value conflicts, will not obscure or reduce all imbalances of power between parties contending about what constitutes good science or appropriate risk management, and will not even get everyone to agree on interpretation of "facts" even if they agree on the facts themselves. Some gaps in knowledge, responses to uncertainty, power, and values are too large to bridge simply with what one says and how one says it, rather than (for example) with what one does.[4] In making these

[4]It is not our mandate to discuss noncommunication means of resolving environmental-management challenges (e.g., NRC 1997; 2004), but a few examples can be useful. The joint fact-finding and analytic-deliberative processes cited in Chapter 4 can narrow factual or values disputes. Stern (1991) suggested that "learning through conflict" could be "a realistic strategy for risk communication" *if* bolstered by a supportive infrastructure (such as, incentives for risk analysts and communicators to resist employer and other pressures, independent evaluation of risk messages, watchdog groups, institutional debates more open to citizen participation, and wider distribution of resources for risk communication). Finally, direct risk-reduction efforts by organizations and individuals (such as, emission controls; favoring nonpersistent, nontoxic inputs to production; and avoidance of possible sources) can minimize some communication challenges if decision-makers believe that such steps are appropriate.

remarks, we do not wish to encourage the view that communication about biomonitoring would be ineffective or inefficient. On the contrary, communication and systematic evaluation of communication techniques has been given inadequate attention in environmental management (Chapter 4). Neither overenthusiasm of supporters, as reflected in unmet (and undeliverable) promises, nor cynicism or apathy should undermine implementation of biomonitoring communication.

In the next section of this chapter, we discuss how "principles" of risk communication provide a good starting point, but details of a communication strategy must be case-specific and tested empirically before implementation. Examples from the literature on lay response to uncertainty and trust in risk-managing institutions demonstrate that point. Then the chapter argues that a proper balance must be achieved between communications seeking to avoid false positives (such as the inference that detection of a biomarker signals inevitable adverse health effects) and false negatives (such as the belief that nondetections or low concentrations relative to a reference range indicate no health problems). The core of the chapter discusses how different groups of biomarkers and thus different kinds and amounts of relevant information can affect interpretation and use. The chapter concludes with practical and research recommendations to enhance the infrastructure for effective communication about biomonitoring.

PRINCIPLES OF RISK COMMUNICATION

Our aim is to inform research and practice on environmental-biomonitoring communication, not to provide a primer on risk communication in general (a few, widely varied, examples of primers include ATSDR 2001; Hance et al. 1988; NRC 1989; Pflugh et al. 1994; Stern and Fineberg 1996). However, a brief background can both inform potential communicators who are new to this topic and put biomonitoring-relevant discussions into context. The extensive practical literature on risk communication can be drawn on for more detailed instruction as needed.

Much attention has been garnered by "principles" of communication that professionals are advised to follow. Well-known examples are seven principles articulated for the Environmental Protection Agency (EPA): accept and involve the public as a legitimate partner (see our Chapter 4); plan carefully and evaluate efforts (Chapter 4); listen to the public's specific concerns (Chapter 4); be honest, frank, and open; coordinate and collaborate with other credible sources; meet the needs of the media; and speak clearly and with compassion (Covello and Allen 1988). Those and related principles have face validity and often practical utility despite their apparent obviousness and abstractness. For example, treating your constituents as though they are ignorant, hysterical, self-interested, or ideologically

driven is no more likely to be effective than if you were treated that way by someone who wanted you to comprehend and agree with his or her message. Thus, one of the first commandments of effective communication is to never assume how any party knows or feels without empirical test. Another is to show respect for each other, regardless of what you think you know about the other's beliefs.

Such principles emerge from practitioners' deliberation on personal experiences, complemented occasionally by systematic observation or experimentation. As with the Golden Rule and its equivalents in other cultures ("Do unto others . . ."), it can be surprisingly difficult to recognize shortfalls in one's performance of principles regarding respect, honesty, clarity, and the like, let alone to modify one's behavior to put them into practice. So repetition of such principles in communication guides and careful attention to them by would-be communicators are by no means superfluous.

However, "rules for risk communication are not enough" (Rowan 1994). There are two critical notions in biomonitoring communication: the need for empirical testing of even the assumptions of the expert or experienced communicator (Morgan and Lave 1990) and attention to situational details that broad principles alone cannot provide and published principles may not even cover. For example, if your goal is to communicate biomonitoring findings to a constituency, what do you know about its members' beliefs, attitudes, behavioral intentions, behaviors, and policy preferences with regard to this topic, in both mean responses and their variability? How are they similar to or different from other constituents on these measures, including those who will hear your conversation without being deliberately included? How do your background and current environment, and those of your institution, limit what you could say or even imagine saying? How aware are you of such personal and institutional limits? How might constituents' or your own limits or flexibility affect communication success? Those and other contextual factors affect whether and how mutual understanding, agreement, and action on biomonitoring data occur; and people charged with such communication must learn the answers to these and related questions. The tension between "principles" and effective communication practices is illustrated in discussion of uncertainty (and variability) and trust.

Uncertainty and Variability

As with other data used to evaluate health risks, uncertainty will characterize interpretation and use of biomonitoring results for years to come, although little is known about how nonscientists deal with technical uncertainties. In general, in their daily lives, people avoid wherever possible

uncertainty about bad outcomes from activities that have small or uncertain benefit; control over outcomes is preferred to the lack of control that uncertainty implies (Edwards and Weary 1998). However, both citizens and policy-makers make decisions in the face of uncertainty (e.g., Lopes 1983); decisions are often rationalized, if not driven, by that uncertainty.

It is common for scientists and officials to believe that they are far less uncertainty-averse with respect to environmental risks than is "the public" (Lopes 1983; Carpenter 1995; Einsiedel and Thorne 1999); for many environmental-health scientists, uncertainty is a professional "given." Many scientists and officials apparently deem citizens unable to conceptualize risk-management uncertainties (Frewer et al. 2003)—a view not shared by this committee. In fact, what little evidence we have suggests that a globally uncertainty-averse public is a myth; responses vary widely across the population (e.g., Furnham and Ribchester 1995). Johnson and Slovic (1998) found that 35% of a college-student sample preferred to know whether a situation was safe or unsafe rather than to get a risk probability or range of risk estimates. Frewer et al. (2002) found that only 13% of their UK sample preferred no information about risk until all uncertainty had been eliminated. They also found a public demand for information on food-risk uncertainty as soon as the uncertainty was identified and a greater public acceptance of uncertainty about the science than of uncertainty due to government's ignorance of the nature or extent of a problem. Those authors concluded that communication should focus on "what is being done to reduce the uncertainty." Miles and Frewer (2003) speculated that communication of uncertainty in risk estimates about a hazard exposure over which people feel they have little individual control might make the hazard seem "out of control" by institutions too, but their study design did not allow a direct test of that hypothesis.

Overall, most risk-communication guides urge open and transparent discussion of uncertainty (e.g., NRC 1989; Hance et al. 1988; ATSDR 2001; also see literature reviews in Johnson and Slovic 1995, 1998).[5] Occasionally, the guides go into slightly more detail. For example, Hance et al. (1988) suggest "be specific about what you are doing to find the answers," "consider involving the public in resolving the uncertainty," "give people as much individual control as possible over an uncertain situation," "stress the caution built into standard-setting and risk assessment," "if people are demanding absolute certainty, pay attention to values and other concerns, not just the science," and "acknowledge the policy disagreements that arise from uncertainty." Despite their and others' discussions of what this advice might mean, however, such principles carry practitioners only so far.

[5]Many reports on risk assessment also stress the value of reporting uncertainty (e.g., NRC, 1994).

Sketchy but provocative suggestions are beginning to emerge from empirical studies of uncertainty in risk communication. Frewer et al. (1998) provided persuasive information about genetic engineering in food production to British citizens who had positive or negative attitudes toward the technology. Half saw a statement of uncertainty; half did not. The statement said "we are reasonably certain that there are minimal risks . . ., we cannot be 100 percent certain. This is true of any scientific process. However, the information provided has been derived from the best scientific information available" (Frewer et al. 1998). The admission of uncertainty increased acceptance and reduced rejection of genetic engineering of human DNA, animals, and plants. People with prior negative views were particularly likely to "find the information more informative if information about uncertainty is included" (Frewer et al. 1998).

Carpenter (1995) noted that "the client/recipient" might prefer "unambiguous predictions and advice" now to candor about uncertainties, but environmental professionals' credibility will disappear if "events . . . show them to be substantially wrong." However, White and Eiser (in press) suggested that trust experiments show that if, in the face of uncertainty, professionals make a "mistake . . . of the right kind [such as a precautionary rather than risk-taking action on the public's behalf, it] could actually make them seem more trustworthy to lay observers because a) it shows they are open and honest and b) people accept that even experts make mistakes sometimes." Thus, the results of communicating about uncertainty depend on the context.

That conclusion is complemented by studies (Johnson and Slovic 1995, 1998; Johnson 2003a, 2004a) that examined how people reacted to uncertainty as expressed in a range of estimates of risk (for example, from 1 in 10,000,000 to 1 in 100,000). As reported by Johnson (2003a, 2004a), the proportions of college-student and working-class industry-neighbor samples that found the producer of such a risk range to be honest and competent ranged from 23% to 49%. Ratings for dishonest and incompetent were 12-27%, honest but incompetent 9-17%, and competent but dishonest 10-20%; 7-18% did not know. The honest-competent inference clearly dominated even without any signal of what (if anything) would be done in light of the uncertainty in risk estimates, although there was no majority view. Adding a precautionary signal (such as, intent to reduce exposure) might increase the proportion that found official discussion or representation of uncertainties in biomonitoring cases to be both honest and competent, just as a clear signal of inaction might sharply increase negative responses. Systematic testing of those and other uncertainty hypotheses is needed because we do not yet know what factors (such as, perceived benefits of hazardous activities) might affect such relations. Empirical examination of principles of risk communication related to uncertainty is in its infancy.

Carpenter (1995) specified four questions that communication should try to answer: What do we know, with what accuracy, and how confident are we about our data? What don't we know, and why are we uncertain? What could we know, if we had more time, money, and talent? What should we know to act in the face of uncertainty? The first two questions are ones that CDC uses when it reports results of site-specific biomonitoring studies (J. Pirkle, CDC, personal commun., May 16, 2005). Both are valuable, but attention should also be devoted, in communication research and practice, to the latter two questions.

Communicating about variability might be less challenging than communicating about uncertainty, although equally important. Anecdotal information suggests that people tend to be aware of or to recognize quickly the concept of variability in susceptibility and exposure, so communicating about variability might be easier than discussing probability and other unfamiliar concepts. Furthermore, uncertainty can be reduced to some degree if sufficient and proper effort is devoted to that end, and failure to undertake uncertainty reduction might undermine trust, whereas variability is immutable (Chapter 4). However, no research has explored those hypotheses, and other aspects of biomonitoring variability (for example, in excretion rates) important for interpretation and use of biomarker data are probably less familiar to laypeople.

Trust

On its face, the topic of trust is more abstract than uncertainty in application to biomonitoring. However, experience and correlational studies suggest that trust in institutions is a critical factor in judgments of how risky something is, and it is likely, in the contentious atmosphere surrounding biomonitoring, that trust will also affect whether nonscientists see having biomarker concentrations in one's body tissues as risky. For example, later in this chapter we point to evidence of skepticism about the protectiveness of benchmarks based on external-exposure monitoring and suggest that it might apply to biomonitoring benchmarks, too.

Interpretations of experience and initial research on "trust asymmetry" in the risk literature (Slovic 1993) suggest that trust is easy to lose and hard to gain. The thrust of the "principles" literature, however, puts practitioners in a bind. They must perform flawlessly to avoid ultimate failure, so it seems, but they have no guidance on building or maintaining trust much more specific than "plan carefully" (plan what?), "listen" (how and to whom?), and the like. More recent research suggests that any asymmetry in gaining and losing trust can depend on the risk object (such as nuclear power vs pharmaceutical industries); studies differ in whether good or bad news has stronger effects on judged risk. Whether trust is

asymmetric depends on such factors as the constituency's attitudes (for example, trusting groups resist bad news, and skeptical ones resist good news) and on whether the good or bad "news" concerns risk-management policies or concrete events (Cvetkovich et al. 2002; White et al. 2003; White and Eiser 2005).

Studies also are beginning to suggest that demonstrating that one shares salient values with one's constituencies—such as preferring to take the risk of creating false alarms (false positives) rather than misses (false negatives)—can build trust (e.g., Earle and Cvetkovich 1995; Cvetkovich and Winter 2003; Siegrist et al. 2003; White and Eiser, in press). For example, a comparison of the same risk at different times (for example, this year vs last year) was suggested to be among the best ways to put risks into context. It was shown empirically that the public ranked it first among 14 comparisons (Roth et al. 1990; Johnson 2003b). However, the message tested also included elements of risk reduction ("Despite the extremely low health risks to the community from emissions . . . at our plant, we are still looking for ways to lower these levels further. These are some of the plans we have under way to accomplish this. . . .") and information-sharing not strictly part of the temporal comparison. With those removed from the text, it dropped to a middle-to-low rank (Johnson 2004b). In other words, it was the promise to keep searching for ways to lower the risk further and to keep the concerned community informed about plant operations that fostered positive reactions, not the risk comparison itself. Those studies differ in the conditions that make value-sharing helpful. For example, some scholars argue that effective demonstration that one shares the constituency's salient values is most important when people are unfamiliar with a hazard (often the case with environmental chemicals). Others suggest that the critical factor is how constituents judge the balance of risks and benefits to themselves; if they see few personal benefits (also commonly the case when environmental toxicants are being considered), a precautionary stance by risk managers becomes more desired. The field is not yet developed enough to provide guaranteed recipes for trust-building. Such recipes may be impossible to provide, given variability in social contexts, and might be undesirable for ethical and democratic reasons. But the studies point the way toward moving beyond general principles to more-detailed advice. Clearly, biomonitoring efforts will vary widely in both need and ability to match the full scope of suggestions for promoting trust, such as the analytic-deliberative processes discussed in Chapter 4 (Stern and Fineberg 1996). But study funders and managers would benefit from considering whether and how their efforts would be enhanced by pursuing trust-enhancing techniques and by empirically testing and expanding relevant communication principles.

TRADING OFF AVOIDANCE OF FALSE POSITIVES AND FALSE NEGATIVES IN COMMUNICATION

Communication challenges are often intimately entwined with risk-management challenges (Chapter 1), and biomonitoring is no exception. Scientists use statistical and other criteria to err on the side of accepting false negatives (they reject a hypothesis that turns out to be true) because they see false positives (not rejecting a false hypothesis) as the outcome more dangerous to science's advance and credibility.[6] In a parallel sense, there is a strong emphasis in current institutional messages about biomonitoring, as well as in concerns about incautious expansion of biomonitoring, on avoiding message recipients' false-positive interpretations (Becker 2005; Duggan 2005; Osterloh 2005; Robison 2005; Schober 2005). For example, government agencies and industry groups have argued that one should warn against inferences that health effects would come from observed biomarker concentrations when (as for most biomarkers) the effects are not certain. Similarly, messages should not imply without evidence that a specific activity is the source of observed body burdens or that particular actions will reduce exposures to environmental chemicals. The assumption in those arguments is that most claims about health effects or sources will turn out to be false positives, so officials do not want other people (such as "the general public") to conclude prematurely that a health effect could occur or a source be responsible. Avoiding the creation of such false positives and possible large negative outcomes is a legitimate risk-management aim that biomonitoring communicators should respect.

However, there are flaws in an *unreflective* emphasis on avoiding creation of false-positive inferences as a result of biomonitoring communications. First, it fails to discriminate between good and bad reasons for fearing that messages will evoke false-positive conclusions. Erroneous assumptions about the psychological, economic, or political fallout of declaring a biomarker concentration as evidence of a public-health threat can lead to misallocation of societal resources. For example, it is an enduring myth among many policy-makers that "panic" is the default response of "the public" to natural, social, and technological hazards, whether hurricanes, terrorism, or "pollutants" in people's bodies. In some cases, individual or collective human responses may be inappropriate, but

[6]For instance, suppose the statistical criterion for testing a null hypothesis is $p < 0.05$. If $p < 0.05$, the researcher does "not reject" the hypothesis, because to "accept" the hypothesis would be to take a greater risk of treating as true a proposition that might turn out to be false. Because scientists have been historically more averse to false positives than to false negatives, they have been willing to "reject" hypotheses rather than take the stance of "not accepting" them.

people rarely exhibit mass hysteria (Wenger 1987). Second, ensuring that messages do not create false-negative interpretations by message recipients also can be an important risk-management goal. Unrecognized threats can be as undesirable as overlooked opportunities, and apathy as dangerous as fear; some claims about health effects or sources will turn out to be true, and we cannot tell prospectively which is which in the face of the uncertainties to which most biomarkers are subject. Obviously, tradeoffs are necessary because false positives (such as inferring health effects from biomarker findings when the effects are nonexistent) and false negatives (such as assuming that biomarker concentrations that cause health effects do not) cannot be minimized simultaneously except in rare circumstances. Third, for communication specifically, a failure during communication planning to recognize its flaws might make a strategy aimed only at avoiding false-positive responses backfire. Countervailing facts, dissenting opinions, and divergent values will tend to emerge, however carefully the communicating organization tries to obscure them (Hance et al. 1988), and the outcome of their emergence may be loss of credibility for the organization and its message (Slovic 1993).

A balanced and forthright communication about what is known, or can be reasonably (or unreasonably) inferred, from biomonitoring data would be prudent (Hance et al. 1988; NRC 1989; Pflugh et al. 1994; Carpenter 1995; Stern and Fineberg 1996; ATSDR 2001). Acknowledging tradeoffs between the dangers of communication that could foster false positives and the danger of communication that could foster false negatives, and explaining why the tradeoff embodied by a specific message was chosen, could reduce constituencies' concerns even if some continue to oppose the tradeoff. Joint decision-making about a tradeoff (Chapter 4), in which biomonitoring researchers partner with their constituencies, is another useful strategy. Putting potential counterarguments into one's initial messages and pointing out their flaws can inoculate constituencies against later criticism (Johnson 2002b). Similarly, acknowledging the wide range of possible interpretations and discussing their relative strengths and weaknesses can undercut the effect of overemphases by contending constituencies on particular interpretations (for example, the disparate responses to CDC biomonitoring reports by stakeholders cited in the introduction to this chapter).

Our goal here is not to dictate acceptable tradeoffs to decision-makers but to make explicit the problems that an excessive emphasis on avoiding creation of alleged false positives might pose. The appropriate balance between having constituents avoid drawing false-positive inferences and avoid drawing false-negative inferences will vary with the aims of a biomonitoring study and the threats of concern to the relevant decision-makers (such as, researchers, sponsors, and subjects). Our intent here is that the

decision on balance be an explicit one, whatever it is, rather than be the outcome of untested stereotypes or absent-mindedness.

DISCUSSING RESULTS BELOW THE LIMIT OF DETECTION FOR BIOMARKERS

One of several examples in this chapter of the "balance" issue is the study that detects no biomarkers. Nondetection could be ideal for everyone except (perhaps) biomonitoring researchers: all else being equal, no one wishes evidence of human exposure to environmental chemicals. Study subjects and wider populations that share their potential external exposures could be told that their exposure is no worse, and perhaps better, than that of the reference-range population.

However, the communication challenge of results below the limit of detection is not quite so easily resolved. Each environmental-monitoring technique, including those of biomonitoring, has a limit in the amount of a chemical that it can reliably and validly measure in a given matrix. Below that limit, it is impossible to tell how much of the substance, if any, is in the sample. Experience with or modification of the technique or invention of a new one can lower the detection limit eventually, but in the short run it is fixed. That is one reason, when multiple biomonitoring methods are available, that "the method chosen can have an appreciable effect on the results and their interpretation" (Helsel 1990, cited by Bates et al. 2005).

A result below the limit of detection is not an indicator of nonexposure, and this needs to be conveyed clearly to lay constituents of biomonitoring. Similarly, it is not necessarily true in all cases, that concentrations below the detection limit will not cause health problems. In the case of external measures of exposure (such as, concentrations in drinking water), public-health standards for carcinogens are commonly set above the value that experts believe to be protective of health (whether that is EPA's zero maximum-contaminant-level goal or the target one-in-a-million risk for New Jersey's drinking-water standards). Because measurements of the health-protective concentration are not reliable, the standard is set at the detection level (or at the level that treatment technology can reliably or cost-effectively reach, if that is higher). Regulators hope that the standard can be set at the health-protective level when technology improves. It would not be surprising if biomonitoring reference benchmarks (Chapter 5) for some chemicals were below reliably measurable levels, and this raises questions about whether results below the limit of detection indicate lack of potential health problems. Study communication about results below the limit of detection should take those issues into account by explaining both the reassuring news of relatively low exposure and the possibility (when applicable) that the health risk might not be zero.

COMMUNICATING HEALTH INTERPRETATIONS OF DETECTED BIOMARKERS

We discuss here issues raised by an inference of health effects when available evidence on health effects of biomonitored substances varies widely in quality, quantity, and applicability to the subject population (see Table 3-1). Depending on the constituency and situation being addressed, investigators' assumptions about whether and how epidemiologic or toxicologic data support the purpose of the biomonitoring project may need to be communicated. The first topic is the mere observation of group II and IV biomarkers in study subjects, which can be reliably measured in humans but lack biologic-effect data or dose-response data. The second topic is comparison of observed biomarker concentrations with reference ranges, which are also likely for group II and IV biomarkers. The third topic is comparison with health benchmarks, which ideally will involve human data (groups V, VII, and sometimes VI) but in some cases (for example, biomarker-informed risk assessment) might entail animal data (groups III and sometimes VI). Finally, we discuss clinical practice, which might involve any biomarker group.

Biomarker Presence Implies Neither Health Effects Nor Their Absence

Public Beliefs About Exposure and Health Effects

The sketchy evidence on lay views about relationships between exposure and health effects suggests that there should be some concern about erroneous health inferences that nonscientists might draw from reports that biomarkers have been detected in human tissues. Nonscientists seem to read a wide range of interpretations and content (including content not explicitly included) into small texts about exposure (MacGregor et al. 1999). For example, "when a [mock] newspaper report about a chemical includes the phrase 'has been found to cause cancer,' the reader may infer that since only an important and serious finding would warrant publication, typical exposures to the chemical must be widespread, pose a significant risk, and should be a matter of some concern" (MacGregor et al. 1999). The same study found that people have widely varied but usually deterministic beliefs about links between cause, exposure, and effect. At least for carcinogens, which many laypeople do not see as having threshold levels for health risk, "the concept of exposure gains its meaning from both the nature of exposure [such as length of contact] and the perceived seriousness of its consequences" (MacGregor et al. 1999). CDC's *Third National Report on Human Exposure to Environmental Chemicals* (2005) cautioned that "concentrations of the chemical are more important determinants of the relation

to disease, when established in appropriate research studies, than the detection or presence of a chemical." However, 36% of a Portland, Oregon, public sample agreed (contrary to that caution) that "for pesticides, it's not how much of the chemical you are exposed to that should worry you, but whether or not you are exposed to it at all" (Kraus et al. 1992; McCallum and Santos 1994).

But biomonitoring data offer potential communication advantages over environmental-monitoring data that should not be overlooked. Sexton et al. (2004) note that they yield "unequivocal evidence that both exposure and uptake have taken place." As a result, state officials said "that human exposure [biomarker] data are often the most valid and persuasive evidence available to demonstrate whether, and to what extent, exposure has occurred or changed over time. In highly charged situations, where community trust has eroded, such data may be the only evidence acceptable to area residents" (GAO 2000). Thus, the 'unequivocal evidence [of] both exposure and uptake' provided by exposure biomarkers offers some rare certainty in a biomonitoring field rife with uncertainties. When communicators report 'what is known' about biomonitoring results, as suggested earlier in this chapter, this is an important point to make, and equally pertinent whether biomarkers are detected or not. However, such an emphasis will need to avoid feeding into any automatic assumption of 'exposure=health effects' among biomonitoring constituents; as noted later in this section, our current ignorance about how to avoid that inference warrants research on how this can be done effectively.

The concerns expressed by some experts and constituents about breastfeeding in the case of the California biomonitoring legislation exemplify the fear that nonscientists will assume that increased (or any) biomarker concentrations in human tissue indicate potential health effects. The extent of the assumption is unclear, although available evidence suggests that it occurs among at least a substantial minority of the public. "If you are exposed to a carcinogen, then you are likely to get cancer" garnered agreement from 36% of the Portland group; 17% said that they didn't know (Kraus et al. 1992). A similar statement received agreement from 62% (3% "don't know") of a national survey of Canadians (Krewski et al. 1995), 43% (13% "don't know") of a college student population (MacGregor et al. 1999), and 26% (14% "don't know") of an opportunity sample of New Jersey respondents (B. Johnson, New Jersey Department of Environmental Protection, personal communication about Johnson 2002b data). It seems unlikely that that reaction will be less common when the indicator of exposure is biomarker detection. To the extent that such a lay view is at odds with the scientific view that exposure data alone do not indicate health effects, it presents an important challenge.

Communicating About Biomarker Presence

We do not know how to convey the biomarker-presence-does-not-indicate-health-effects message effectively. The anecdotal evidence that large surveillance-study results (such as the National Health and Nutrition Examination Survey, NHANES) no longer excite great public attention except where people identify a possible local source might reflect the efficacy of CDC's and others' efforts to convey this message. However, apparent quiescence might just as well reflect lack of salience, poor measures of public concern and action, a (temporary) fatalism because people see no effective means to prevent or reduce such exposures, or a lack of serious effort by institutions to take such actions or inform the public about them. If current no-health-effects messages are *not* effective, one might do better to apply a "mental-model" approach to developing messages (Morgan et al. 2002). That approach, in this case, entails identifying the beliefs (accurate and important, accurate and trivial, misconceptions, biases, and so on) that constituencies hold about the causal process by which exposure (external or internal) leads to health effects. It would entail intensive interviews that begin with nondirective questions (for example, "Tell me about environmental chemicals in human blood, urine, or breast milk") followed by questions informed by scientific views of the causal process.[7] Later large-scale surveys reveal the relative prevalence of particular biomonitoring views in the population. Messages are then designed to identify incorrect views, explain why they are not correct (Rowan 1994), and provide "correct" views (which, depending on the topic, could be definitive statements or merely clarifications of scientific uncertainties and disagreements and the reasons for them). In referring to 'correct' views, the committee considers that experts and laypeople can be educated by properly designed "mental models" research, as in exploring expert disagreements (see footnote 7) or in learning about lay beliefs and concerns, such as about exposure pathways (for example, more than one risk assessment has overlooked residential garden vegetables). The committee does not intend this concept to imply only one-way communication and learning about the general public's views, but supports examining the views of experts, risk managers, and the general public.

[7]We do not imply here that scientists know all cause-effect relations for human biomonitoring; in fact, the mental-model technique probably becomes more useful as it makes expert uncertainties and disagreements more explicit. However, experts' mental models of the causal links are likely to be more comprehensive than those of nonscientists and thus provide a useful guide for topics on which to probe lay mental models about biomonitoring and biomarkers.

For example, many people seem to hold a one-hit "mental model" of carcinogenesis; 58% of Canadians in a national survey disagreed that "the body usually repairs the damage caused by exposure to radiation so that cancer does not occur," whereas only 31% agreed (Krewski et al. 1995). However, beliefs about what exposure means vary widely, so the proportion of people who felt that exposure to a carcinogen had "definitely" occurred was over 90% for daily smoking of one pack of cigarettes, over 40% for 10 minutes in a smoke-filled room, and 34% for smoking a single cigarette (MacGregor et al. 1999). Explaining the multiple-hit model could help people to understand that a single "exposure" to a carcinogen will not in and of itself cause cancer. Analogies (such as the fact that one exposure to someone with the flu does not inevitably mean getting the flu oneself) also might help if both communicators and their constituencies see the analogies as legitimate comparisons (e.g., Covello et al. 1988; Roth et al. 1990; Johnson 2003b, 2004b). Use of qualifiers (such as the idea of exposure to "an extremely small amount" or instances of small exposures, such as smoking only one cigarette or pumping one's own gasoline just once) may be needed for most people to agree on exposure magnitudes. The term *exposure* alone may not be enough to convey the concept (MacGregor et al. 1999).

Expert Disputes About Health Implications

Any such messages must account for expert disagreements on exposure-health linkages if such disputes could affect the credibility or lay understanding of biomonitoring results. The mental-model approach to risk communication was developed on the presumption that experts' equivalent models would constitute a "gold standard." Expert consensus and good reason for high confidence occur in many fields, perhaps including some aspects of biomonitoring. Yet expert certainty and consensus are neither universal nor infallible. Although the advocates of the mental-model method acknowledge the need to grapple with expert disagreements (Morgan et al. 2002), we need more effort in this regard (Johnson 2002a). The public does not appreciate disputes among scientists over risks and tends to attribute them to incompetence or self-interest (for example of experts' employers) rather than to limitations of available evidence (Johnson and Slovic 1995, 1998; Johnson 2003a). Studies of ways to communicate conflicting experts' views are few (e.g., Renn et al. 1991 on the group Delphi approach), and we do not yet know what will both reduce distrust and increase knowledge. But even implicitly portraying expert opinion on disputed topics as united is likely to have poor results for practical communication and ethical goals. Constituents' discovery of expert disputes is highly likely, and the perceived coverup will undermine future relations.

Health Effects Cannot Be Ruled Out

The message that biomarker data alone do not indicate health problems is incomplete, if necessary, and should not stand on its own. Without reasonably definitive data demonstrating the absence or likely absence of health effects due to observed magnitudes of exposure (such as well-done epidemiologic studies of the same or a similar population or reliable benchmarks), such a statement could be correct in denotation but false in connotation. In other words, it would imply that health effects have been ruled out when in fact they had not been sought, that there was no current method for observing or predicting such effects at these levels, or that available data were equivocal. Absence of evidence of effects is not identical with evidence of absence of effects—a distinction that must be clear to constituents. Otherwise, there is a large practical communication and ethical risk attached to simply saying that the presence of chemicals in human tissue does not imply health effects. In many cases biomonitoring uncertainties will mean that the appropriate scientific conclusion will be 'high biomarker levels are not necessarily bad, low levels are not necessarily good.' Empirical research will be needed to determine how to convey that conclusion appropriately, which might require supporting information (for example, on exposure reduction options) to avoid undue concern or apathy among constituents.

Some people might be confused by that message. For others, it might evoke both comfort and anxiety, perhaps to the extent that anxiety swamps reassurance (Otway and Wynne 1989). Still others will find it difficult to hear the presence-does-not-imply-health-effects message; they would be vigilant about group II and IV biomarker-related health effects even without the caveat about not ruling out such effects. However, the varied responses cannot justify omitting an accurate and useful interpretation.

We have already presented ideas on how to discuss uncertain data and how willingness to discuss uncertainties (including those in health effects) could promote trust. As noted in Chapter 4 on ethical grounds, providing information on steps that people can take to reduce their exposures to a chemical, regardless of uncertainties about health effects, allows them to take action if they so choose. In addition, risk-perception research shows that providing a sense of individual control over potential threats by giving people options for individual action is often a good way to reduce perceived risk as well (e.g., Hance et al. 1988; Slovic 1993). Sometimes, the mere fact that such information is available can reassure people enough to forestall such personal action. Provision of personal-action suggestions, however, may not avoid demands for institutional precautionary action. Other techniques may help to reduce rejection of information that seems threatening. Thinking about one's own mortality—perhaps fostered in some people by

information that they or people similar to them have chemicals in their bodies—can make people defensive about their values and identities and thus resistant to countervailing information (Jonas et al. 2003). Asking people to deliberate on important values (for instance, asking them to rank several values and then write a little essay on a time in their life that exemplified their most important value) reduced their resistance to applying messages about health-protection behaviors to themselves (e.g., Sherman et al. 2000). Translation of "values affirmation" and other denial-reducing techniques for practical use in public-health communication is worth pursuing.

Miscellaneous Issues for Group II and IV Biomarkers

Two other health issues related to the mere reported presence of biomarkers of environmental chemicals deserve mention here; they involve mixtures and difference in exposures and susceptibilities between populations. First, as detection limits decrease and the number of biomonitored chemicals increases, reports of multiple chemicals in "bodies in general," if not "in my body," might arouse concern without regard to concentrations, types, or sources. We do not know to what degree laypeople have mental models that include additive or synergistic adverse health effects of multiple chemicals, but anecdotally it seems unlikely that their mental models include antagonistic or health-enhancing effects of mixtures. Experts have not gathered enough data on effects of mixtures (biomarker-related or not) to have stable, consensual mental models of their own on this topic. CDC does not report personal body burdens of environmental chemicals—partly, it seems, because of concern about precisely this potential perception, partly because the hundreds of chemicals that it now tests for are not tested in every subject. Thus, we are at the mercy of anecdotes and probably incorrect inferences.

If CDC reported the individual body-burden data that it now has (see Chapter 5 recommendation), even with caveats this could help to address communication, as well as technical needs. Assuming that expert knowledge about mixtures will be lacking for some time to come, messages need to emphasize how big a problem (if any) such interactions are likely to pose and what efforts are being made (even if not by the specific study at hand) to get more definitive answers. Laypeople will grudgingly accept messages about uncertainty (presumably including effects of mixtures) if they can be assured that something is being done to reduce the uncertainty. Supporting messages would address ever-lower detection limits and expansion of the scope of biomarker surveillance, as with analogies (for example, changing from grosser-weave nets or sieves to finer-weave ones to explain that most, if not all, of the "new" things were probably already there—also see Chap-

ter 5 on historical-use information—but that earlier technology could not capture the smaller "fish" or "particles"). Data are also needed on how laypeople understand or respond to notions of detection limits or the scope of surveillance efforts and on their views on the effects of exposures to chemical mixtures on health.

The second issue for talking about biomarker concentrations is different exposures and susceptibilities across populations (such as those defined by sex, ethnicity, or income); "what is considered 'healthy' in some individuals might indicate a health risk in others" (Schulte and Talaska 1995). Experience has shown that the American public is rather familiar with the concept of variability in exposures and susceptibility (see earlier discussion)—for example, people will ask, in effect, whether health standards for drinking water take into account the greater consumption per body weight of infants and children. The limits of expert knowledge about the nature and degree of such variability motivated our recommendation for collection of data on socioeconomic status as part of biomonitoring studies (Chapter 4). Communication will need to take account of what is known so that messages (such as the biomarker-presence-does-not-mean-health-effects message) are sent only to populations for which they are valid. Yet, in general, there is no reason at this point to presume that communication with women, ethnic minorities, or other populations, which might have different exposures or susceptibilities from that of the general population, should differ from communication with any other constituents. Respect, attention to constituent concerns and questions, and careful crafting of messages to address constituent beliefs work with any constituency, including those whose particular exposures or susceptibilities should be kept in mind in interpreting biomarkers' health implications.

Comparisons with Reference Ranges

The next step up from the no-necessary-health-effects message in communicating about biomarker detection is to compare detected concentrations with reference ranges. This also occurs for group II and IV biomarkers but depends on the added availability of studies in reference populations. Strictly speaking, such comparisons concern relative exposures rather than health effects (see Chapter 5); however, in the absence of relevant health information, it appears to be a common strategy to use them to imply the *likely absence* of health effects. If subjects in a given study exhibit concentrations lower than, or at least no higher than, a reference range, by implication (according to this approach) they should not exhibit *unusual* health effects relative to the reference population. CDC found that people seem to appreciate learning that "your value [or the mean value for the demographic group to which you belong] falls below what 95 out of 100 people

have" or "you have values three times those of the general population but [more or less than] this occupationally exposed group" (J. Pirkle, CDC, personal commun., May 16, 2005).

Despite the reported appreciation, there are dangers in transmitting such messages. For example, Sexton et al. (2004) asserted that "if average levels among the cohort are similar to those of the general public, then the group's exposure is unlikely to cause unique problems." Yet similarity of averages (and which kinds?) in two groups does not necessarily denote similar distribution of exposures. Nor does inference that problems among study subjects are unlikely to be "unique" mean that no problems should be expected in response to that exposure in either group. "You're no worse off than anyone else" is not a conclusion that will or should reassure everyone.

Biomonitoring publications variously define a reference population as having "no," "only minimal," "some," "nonoccupational," or "typical" exposure to the target substance (e.g., Pirkle et al. 1995; Schulte and Talaska 1995; GAO 2000). Depending on the substances and populations involved, the resulting reference ranges could differ widely and thus promote quite different inferences about results in the study population. In particular, the implication that below- or within-range concentrations of tested toxicants in a study sample are free of adverse health outcomes is more plausible the more demonstrable it is that the reference population lacks substantial exposure. Thus, it is important for the nature of population sampling and exposure data (if any) to be made clear in communication.

The NHANES sample is generally drawn to reflect the national population as a whole, with external exposures neither measured nor used as part of the sampling frame. That makes it somewhat problematic as the basis of reference ranges to which other samples might be compared. Without exposure measures or reasonable dose-response data or other health benchmarks, it is difficult to conclude that people at the higher end of the NHANES range are "out of trouble" with regard to potential health effects and thus that only study subjects above that range merit concern. CDC has decided that this problem can be avoided by using the 95th percentile as the basis of comparison. In a population as large as that of the United States, that means that more than 5% of 297 million people (as of the middle of 2005), or nearly 15 million people, would have to be exposed to a contaminant source in order to be "in trouble" within the NHANES reference range (J. Pirkle, CDC, personal commun., May 16, 2005). If the sources of a given chemical are concentrated, this is and should be reassuring with respect to relative exposure of biomonitoring subjects who are below the reference range's 95th percentile. However, Chapters 4 and 5 discuss several problems with an exclusive focus on the 95th or high percentiles of reference populations, as well as with reference ranges in general, that should be accounted for in communication on this topic; for example,

reporting the low end of the distribution can be informative for communicating exposure differences, risk-reduction potential, and such factors as excretion-rate capacity that might affect biologically effective doses.

In short, biomonitoring communicators should not extrapolate from relative exposure to the absolute likelihood of adverse health effects. Comparison of study with reference-population biomarker concentrations cannot be informative about such likelihood, for reasons discussed at length in Chapter 5. At best, such comparisons can inform only about relative likelihood, and even then caution is warranted.

Comparisons with Benchmarks

This section discusses communication issues raised by group V-VII biomarkers (Chapter 3), in which some indicator of concentrations at which health effects do or do not appear could be used as a benchmark for the observed biomarker concentrations.

As discussed in Chapter 5, benchmarks based on relevant populations, health end points, and internal doses (or plausible external doses) can be beneficial to study subjects and other concerned publics in evaluating individual and group biomonitoring results. For example, benchmarks could help to dampen health concerns that might otherwise be unduly high because of default lay beliefs about links between chemical body burdens and health outcomes. Conversely, exceedances of such benchmarks can be a signal for more attention and perhaps exposure reduction and other protective actions.

However, the earlier discussion highlighted technical weaknesses of the use of some benchmarks (such as undue extrapolation from occupational benchmarks to more general populations) that raise communication concerns and would need to be explained if the benchmarks were used. For example, CDC has mentioned Biological Exposure Indices (BEIs) for substances for which they are available, warning that these occupational values are "not appropriate" for the general population and are provided "for comparison, not to imply that the BEI is a safety level for general population exposure" (CDC 2005). That is a subtle distinction that may escape many constituencies. People tend to presume that they are being given information (whether in a conversation or in a government report) because it is useful (see also the discussion above of lay reactions to mock news stories about exposures). Many are likely to infer that they could be given such a comparison only because the BEI says something about the likelihood of health effects or about their need to worry. For a few constituents (such as those with physical conditions and health histories similar to those of workers), the BEI comparison might be worthwhile. For others, the communication costs of using a benchmark of uncertain relevance are likely

to outweigh the benefits of providing the BEI as perhaps the only available benchmark for health effects.

The question of whether to treat a benchmark value derived from human or animal data on the relation between a biomarker and a biologic response as a "bright line" (for example, between "safe" and "unsafe") will remain contentious. In clinical and environmental communication *practice*, some physicians and officials feel no compunction about using reference values as just such bright lines. Some nonscientists appreciate such conclusiveness and do not wish to hear about uncertainties and other warnings (see above uncertainty discussion). However, treatment of a benchmark as sharply demarcating good and bad conditions is technically false, and doubt about official statements increases if they stress safety rather than danger (e.g., Weinstein 1986; Kraus et al. 1992; Siegrist and Cvetkovich 2001; Johnson 2003c; White et al. 2003). There is a difference between use of a benchmark for regulatory or litigation purposes, in which the bright-line approach is warranted, and its use for purposes without a structural context that requires definitive conclusions. For example, for external doses it is a legal violation when a utility's water exceeds a drinking-water standard, as determined by mandated measurement protocols. Being ambivalent or ambiguous about what constitutes proper and improper conditions here defeats the purpose of efficient and equitable enforcement of the rule. However, for purposes of explaining potential health consequences, the standard is less clear. It may not have been defined entirely by avoidance of health outcomes (as when there are problems of detection limits or technologic or economic feasibility), and there are differences in standard-setting between carcinogenic and noncarcinogenic contaminants. Thus, even in the regulatory realm it can be misleading to use a benchmark to distinguish between "safe" and "unsafe" exposures for purposes of communication, however appropriate or prudent this use might be for legal purposes.

The bright-line approach to biomonitoring communication is likely to be even more problematic than extrapolation from animal data, the use and calculation of thresholds for noncarcinogens, and the avoidance of thresholds for carcinogens characteristic of benchmark-setting based on external doses (particularly because for some time to come biomarker benchmarks will come from external-dose assessments). Use of "acceptable risk" as an official interpretation of below-benchmark exposure can outrage people who object to having someone else decide what is "acceptable" for them. This is different from government deciding at what concentration no further action by government is needed. A related problem is that people interpret the phrase *very low probability* so variously that it may be as likely to confuse or alarm as to reassure (MacGregor et al. 1999). Empirical testing of methods to convey these concepts without falling into such communication traps is needed. For above-benchmark exposure, use of mes-

sages (as appropriate) that expert uncertainty about health effects diminishes as exposure gets further above the benchmark and that a carcinogen proved in animals may not be proved in humans may help to forestall undue expression of the bright-line syndrome among biomonitoring constituents.

Use of benchmarks is complicated by our ignorance of how lay constituencies perceive them (Johnson and Chess 2003). Among working-class residents near New Jersey factories, equally high concern was prompted by post-treatment concentrations of a contaminant that were 95% or 50% of the health standard. Sketchy findings from other populations suggest that most people are reassured by external-dose exposures (concentrations of substances in ambient air or drinking water) below those allowed by standards, but a substantial minority are concerned by below-standard exposures. In contrast, although most people see above-standard exposures as at least potentially harmful to health, a minority is not concerned about such exposures, at least not if they are only slightly above the standard. Research (B. Johnson, New Jersey Department of Environmental Protection, personal commun., 2005) with more highly educated New Jersey residents confirmed that a substantial proportion exhibited maximum concern below the standard (for example, 24% at half the level of the standard; 39% at 95% of the standard; and 48% at the standard). That study also revealed an unexpected additional perspective: an optimal range of concentrations bracket the standard, with higher or lower values being of more concern, and these study participants want to know the values defining the optimal range rather than just hear a single number. Measures (direct and indirect, qualitative and quantitative) of the frequency of this "optimal" view were inconsistent, and none of the studies involved random national samples. However, for our purposes, the main point is the diversity of public views on benchmarks and their divergence in many cases from the views of scientists and officials, underlining the need for the committee's research recommendations at the end of this chapter.

Reasons for the disparate views have not been explored systematically. They might include distrust in government and other institutions in general, concern about uncertainty in measurement of environmental exposure or in calculation of dose-response relationships, experience in seeing standards revised downward (but never upward), belief that standards incorporate such "illegitimate" considerations as cost and detection limits as well as health effects, and suspicion that expert disputes over standards or risk estimates reflect incompetence or employer self-interest rather than limits of scientific knowledge (Johnson and Chess 2003; Johnson and Slovic 1998; Johnson 2003a). The optimal-range belief might be based on an analogy with medical blood-test results or with nutritional experience (such as minimal daily requirements of vitamins combined with toxicity at higher doses);

the secondary (nonregulatory) standard for pH in drinking water is an optimal range, although few people would know this.

Whatever the reasons for those views, biomonitoring messages must address potential constituent concerns and offer honest explanations as alternatives to the more skeptical ones some members of biomonitoring constituencies may produce on their own. Distrust might be handled by referring people to information sources that are seen as independent and honest. Another trust-building technique is to give people more direct control over information or protection (as in personal radiation dosimeters distributed to neighbors of Japanese nuclear power plants or the personal exposure-reduction advice discussed below) when feasible. Part of public concern about below-benchmark exposures in particular might stem from belief that institutions do not share the precautionary, risk-averse values of their constituencies with regard to the largely involuntary hazards that laypeople see environmental chemicals as representing. The institutions might consider ways to represent their precautionary stance honestly (for example, in exposure-reduction efforts, as discussed below) as a means to make biomarker benchmarks more credible, in addition to such communication alternatives as educating people about natural and other nonindustrial sources of environmental chemicals.

Recent papers on European attitudes toward real or hypothetical precautionary measures regarding health risks posed by mobile telecommunication handsets and towers or base stations (Timotijevic and Barnett 2006; Wiedemann and Schütz 2005) suggest that such measures might not reassure concerned publics and might even raise perceived risk as cues that the risks might be real. Although anecdotal experience and trust research (e.g., White and Eiser, in press) suggest that this will not be a universal reaction to precautionary approaches to environmental biomarker findings, the European results imply two warnings. First, constituent reaction to proposed precautions, as well as constituent suggestions for appropriately reassuring precautions, should be explored before precautions are announced or implemented. Second, it is likely that constituent views of precautions will vary both in kind (for instance, "things must be really bad if they're actually doing something" vs "this is the protection we expect from officials") and among action types or substances, so communication on this topic must be prepared for diversity.

Caution should be used in relying on benchmarks as a means to put biomonitoring findings into a health context. Van Damme and Casteleyn (2003) made the following comment about occupational health, but it applies as well to nonworker situations:

> Health protection cannot always be ensured by simply complying with one or a few biological limit values. Health status of an individual worker

is the result of the integrated effect of many variables, one of which is the exposure to toxic substances in the workplace. A reductionistic approach will fail to offer appropriate protection.

The challenge is complicated by the possibility that there will be a set of potential "comparison values" for a given substance or that a benchmark may be useful for some applications but bad for others (see Chapter 5). Explanation of other potential benchmarks and why they are not suitable in this case may be warranted; in some cases (such as local or national surveillance studies), partnership with other entities (Chapter 4) may help to get agreement on which benchmarks to apply, and disputes over interpretation of results will decrease.

Interpreting Biomarker Findings in the Context of Clinical Data

The best opportunities for communicating health implications of biomonitoring data arise when an unequivocal internal dose-response relationship has been established for humans (by methods discussed in Chapter 5) or when a clinician has data on a person's health that can be used for context-setting. The first case applies primarily to group VII biomarkers (and, with caveats, to some group VI examples); the second case extends to group V biomarkers.

It is challenging to extrapolate general surveillance data, particularly with limited health-effects data, to individual risk estimates without the genetic, external-exposure, lifestyle, and other data that a clinician could use to adjust population risk estimates for individual cases. As a result, previous comments about communication difficulties with respect to health implications apply far more to surveillance studies than they do to the interaction of a personal or occupational physician with an individual patient or worker on whom the physician also has extensive nonbiomarker information. For example, clinicians might in rare cases determine that BEIs are appropriate comparison values for a specific patient's biomarker concentrations.

The greater ease of clinical communication about biomarkers and health than of other biomonitoring communication comes with several caveats. First, not all clinical communication involves people who were study subjects; for example, announcement of local (if not national) surveillance results might prompt members of the wider population to visit their doctors for consultation. The experience of environmental-risk assessors in communicating the distinction between population risks (the usual focus of risk estimates) and individual risks does not augur well for either professionals' ability to communicate the difference well or constituents' ability to comprehend. Second, some people subject to biomonitoring (including those

who order biomarker tests themselves or through their doctors) may have been subject to lower-quality tests or less-informed consent, which may have presented their physicians with challenges that the doctors had trouble recognizing. Third, most doctors are notoriously ignorant about environmental exposure and health issues (e.g., American College of Physicians 1990; Grupenhoff 1990; Goldman et al. 1999; Wynn et al. 2003), and increasing pressures on their time in medical school and practice offer little hope for swift resolution of this problem. Biomonitoring, because it deals with internal doses, might have a better but still small chance at gaining doctors' attention and comprehension than other environmental-health topics. Bates et al. (2005) cite some helpful resources for physicians, such as medical toxicologists (ACMT 2006) and pediatric environmental-health specialty units (ATSDR 2005), but efforts must be made to make doctors aware of them and to use them. Fourth, communication between doctor and patient is often problematic, even without the time pressures of the current U.S. clinical visit. There is a growing literature on doctor-patient communication problems and solutions (e.g., Rimer and Glassman 1998; Schwartz et al. 1999; Alaszewski and Horlick-Jones 2003; Maynard 2003; O'Connor et al. 2003; Paling 2003), but it will take time for this literature to influence clinical practice.

RECOMMENDATIONS

There is no easy recipe for good biomonitoring communication, even if we were dealing with only one kind each of population, biomarker, health effect, reference range or benchmark, exposure pathway, exposure source, biomonitoring study, initial communicator, and constituency and if we had good information on each of these. Given that those conditions do not apply and given the dangers of extrapolating unduly from seemingly similar situations, we do not encourage nor have we promulgated any such recipes. Situation-specific, empirically driven understanding and testing of communication options are vital. However, implementation of several general practical and research recommendations also would enhance the practice of biomonitoring communication. These are listed in rough order of priority for practice and research, respectively.

Practical Recommendations

The research proposed in the next section is critical for systematic development and evaluation of improved biomonitoring communication. However, even without such research, effective implementation of the practical recommendations listed below would go a long way toward improving both the performance and the comfort level of biomonitoring communicators.

Promote Communication Funding and Good Practice. All too often in current biomedical and environmental research and practice, no attention is given by sponsors to communication issues or funding, so the proposals they receive for studies also ignore them (for example, McCallum and Santos 1996). By implication, communication is either relegated to institutional review board review of informed-consent forms or is to be performed (without funding, training, expertise, or planning) in the interstices of the technical tasks of the project. This action by omission is a recipe for bad communication. Without strong institutional support for communication planning and evaluation in individual studies and without development of communication infrastructure generally, biomonitoring communication will become at best unhelpful and at worst a barrier to effective interpretation and use of biomonitoring data. Occasional creative solutions will die for lack of support and dissemination. Biomonitoring sponsors of all kinds (agencies, corporations, foundations, activist groups, and so on) should take the lead in promoting and funding of communication. Sponsors should require explicit planning of communication (Chapter 4); study-specific evaluation of communication (Chapter 4); documentation of communication methods, messages, evaluation methods, and results; and wide distribution of communication materials and findings to the biomonitoring community (not only peer-reviewed academic publications) so that each study need not start from scratch. In a more ambitious approach to information–sharing, a sponsor or consortium of sponsors would establish a biomonitoring-communication database to be maintained and updated for the benefit of the national and international biomonitoring community. In addition to its practical use, biomonitoring-communication researchers might use it for retrospective analyses or to help to set up cooperating networks of practitioners for prospective research (for example, testing one kind of message against another).

Use Consistent Terminology and Concepts. Consistency of usage is needed within and between projects (see above on varied definitions of reference populations, for example). This is a recommendation that can be implemented quickly and relatively easily. Ultimately, this should become part of a larger effort to train various constituencies on what biomonitoring can and cannot tell one about environmental chemicals in humans. Both efforts are vital if there is to be any hope of establishing a minimum of shared knowledge among constituencies so that communicators eventually will not need to recapitulate the entire spectrum of education for each new project.

Expand Biomonitoring Education for Constituents. Depending on educational gaps identified in proposed research, appropriate institutional actors, such as government agencies and university staff, should provide simple, standard background information that will help people to under-

stand how to interpret biomonitoring results that might appear in the mass media and to decide whether and how to pursue informative independent biomonitoring of their own environmental-chemical body burdens. This generic effort will complement project-specific use of consistent terminology and concepts. The usual warnings about systematic development and evaluation of communication apply to these educational materials.

Support Communication Training. Communication training for institutions, organizations, and professionals is particularly important, and it will become more vital once research makes such training more than drilling in communication "principles." Personal and institutional barriers to good practice by doctors, officials, and experts need to be addressed, and training is necessary, but not sufficient, for that task. If partnerships (Chapter 4) with research subjects or other people are envisioned, all parties (including citizens) need some time to learn, both individually and collectively, "how to do it." Practices that "work" in other contexts, such as conventional public hearings, do not help much here, and citizens are as unfamiliar with appropriate behavior in partnerships as are institutions (Renn et al. 1995). Yet training is as neglected as any other communication issue in environmental practice or funding. Anecdotal data suggest that people assume that communication is either something anyone can do without training or obtainable from press-office advice; neither is true.

Document Risk-Reduction Options. Given the potential importance of exposure-reduction actions for both ethics and communication and for both citizens and officials, it is important that there be documentation and wide distribution of information about steps that individuals, communities, and private and public organizations could take to reduce external exposures that might or do contribute to observed biomarker concentrations. Good communication practices mentioned elsewhere in this chapter and in Chapter 4 are as vital to clear and credible communication of exposure reduction information as communication of any other biomonitoring topic. That information should include, whenever available, sources of each environmental chemical and their relative contribution; types of exposure-reduction actions that individuals, households, and institutions could take; and absolute and relative strengths and weaknesses of the actions, such as effectiveness for a given source, cost, and cost effectiveness. The information must be updated to account for new research, innovative technology, and social changes. CDC's biannual reports on human exposure to environmental chemicals now include information on each chemical's uses and sources but too generically to be much more than a start for deciding whether and how to act. Exposure-source and -reduction information is unlikely to come from biomonitoring projects themselves in most cases, so other researchers and institutions must provide information on exposure reduction that will be useful for biomonitoring-study design, communica-

tion, and ethics. The aim of the documentation is not to endorse either exposure reduction in general or specific actions but to help people to identify quickly whether and which exposure-reduction actions, collective or individual, might be appropriate in a given situation. Ideally, there will be a central clearinghouse for such exposure-reduction information because a more laissez faire approach to the distribution of relevant information might not match the need to know and could create communication and ethical problems. Study managers must adapt any general advice to their own cases, so we urge managers to include discussion of their adaptations in their documentation and distribution of communication efforts, so that future biomonitoring studies can benefit from the creativity of their predecessors.

Research Recommendations

All the following recommendations are expected to be valuable for the advancement of biomonitoring communication. However, the first three listed should be particularly fruitful because they should be mutually reinforcing: knowing the biomonitoring-related beliefs of communicators and constituents allows evaluation of current and development of alternative communication messages, and evaluation of current and alternative messages feeds back into understanding of what people believe and thus how to improve communication.

Identify Mental Models of Exposure and Health Effects. The direct and indirect links between external dose, biomarker concentrations, and biologic effects (Figure 3-1) are the core of both exposure biomonitoring and biomonitoring-communication research. Probing for beliefs about specific subtopics (such as chemical mixtures' effects on health, pharmacodynamics, and variability in susceptibility) pertinent to biomonitoring communication will need to be part of the effort. We need a better grasp of the mental models of the linkages held by *all* parties to biomonitoring communication. Studies of the views of lay, "general-public" constituents are important, but so are those of experts, institutional risk managers, and others. That expansive approach is justified by the need to know the expert consensus on causal linkages as a "gold standard" for building messages about the links; any expert disputes that will need explanation to nonexperts (and, perhaps, foster steps toward scientific resolution of the disputes); how, if at all, those who are neither experts nor the general public (such as most institutional officials interested in biomonitoring) differ in their views of causal linkages; and how communicators' similar or different beliefs about the linkages will affect whether communication succeeds or fails. That information will inform both experts and lay people about technical and nontechnical issues related to biomonitoring, and will determine whether it

is feasible to develop and evaluate generic, rather than project-specific, communication designs.

Assess Current Biomonitoring Communications. Research to identify the current nature and scope of biomonitoring-related communications by various organizations, including retrospective analyses of generic and project-specific informational materials, will be a vital complement to the prospective evaluation of new project communications recommended in Chapter 4. For example, the apparently growing phenomenon in which individuals contract with a testing laboratory to measure biomarkers in their urine or blood independently of any formal study (Chapter 2) raises communication concerns. Most people are unlikely to have the background to know what to demand of laboratories in terms of tests, quality control, or interpretation, and it cannot be expected in this for-profit, narrow-margin sector that the laboratories themselves will undertake thorough communication efforts. But without systematic analysis, we do not know whether or what deficits exist in current communication by laboratories, so we cannot work to correct them. Similarly rigorous analyses of biomonitoring-related communication by citizen activists, university scientists, industry (for both occupational and environmental issues), and environmental and public-health agencies at local, state, and federal levels of government are also needed. Despite its increasing experience, for example, even the mass-media strategies of CDC in announcing results of its national surveillance reports might be improved (and inform the work of others) if given careful study. Inconsistencies and gaps among the various organizations' efforts can be identified as targets for remediation or explanation. Furthermore, experience shows that communication may be at odds not only with the beliefs of their intended audiences but also with the mental models of the communicators themselves. That is, the mental models of the communicator might aim at reassurance and clarification, but the actual communication materials do not exemplify reassurance, clarity, or topical relevance even to sympathetic colleagues, much less to intended constituents. Thus, comparison of such materials with the mental models of originators and recipients can be informative.

Identify Reactions to and Effective Messages About Uncertainty. Some relevant topics (such as trust) will continue to be the subject of considerable research outside the biomonitoring field and might in turn be applicable to biomonitoring efforts without much adaptation or supplementation. That is unlikely to be true of the perception of and communication about uncertainty, which despite its centrality to environmental-health issues generally has attracted little researcher attention in the last few decades. Furthermore, only some aspects of biomonitoring-relevant uncertainty are shared with other health or environmental topics. If biomonitoring sponsors do not fund this critical research, it is unlikely to be sponsored by others.

Particular questions important to biomonitoring include these:

- Which of the myriad uncertainties in biomonitoring are of most concern or most difficult to understand? For example, are laypeople more interested in reduction of uncertainties about biomarker-effects relations or exposure-biomarker relations?
- How can these uncertainties best be explained—for example, with verbal vs numeric formats (PCCRARM 1997); Carpenter's (1995) four questions?
- How can alternative lay explanations for uncertainties (such as incompetence or self-interest of experts) best be addressed?
- What are the best means to convey that exposure need not mean health effects, given existing lay beliefs about the exposure-health link? What are the best means to convey that low or typical biomarker concentrations do not rule out health effects?
- Can values affirmation and other techniques to reduce resistance to messages of personal relevance (such as exposure and exposure reduction) be applied in nonlaboratory situations and populations?
- How do comparisons with necessarily uncertain reference ranges (for example, "less than 95% of the population") affect beliefs about exposure, or comparisons with necessarily uncertain benchmarks affect beliefs about health effects, and thus in turn affect the credibility of biomonitoring communication?
- Do discussions of uncertainty affect judgments of the discussant's honesty and competence differently, depending on whether action or inaction is proposed as a consequence of the uncertainty?
- What are the best ways to communicate biomonitoring results when science is unable to determine any interpretation of the data (such as health effects of mixtures)?

Identify Mental Models of Exposure Reduction and Risk Managers. The mental-models method was developed to identify how experts and lay constituencies conceive of causal links in the development of hazards, including the exposure-effects link that is so central to biomonitoring, and how these conceptions and differences between the linkages might affect risk communications. One of the goals for systematically identifying potential reasons for communication failures was to develop subsequent messages that would help laypeople accurately identify institutional or personal actions that would prevent such effects. The method is technically capable of identifying relevant beliefs about risk management as well, but its advocates have done little in this direction despite evidence that such beliefs could have a dominant effect on risk judgments. Although, as mentioned earlier, related trust research does not depend entirely on biomonitoring

funding, additional work will be needed to make some of it applicable to that field. For example, such research often uses abstract institutional stimuli, such as "the federal government" or "information provision," that are not useful (Earle and Cvetkovich 1995), and biomonitoring includes actors (such as private laboratories) that are rarely included in these studies. Probing for exposure-reduction and risk-management beliefs will identify whether precautionary exposure-reduction action by institutions or exposure-reduction advice to individuals reduces or increases judged-risk magnitude, concern, or trust among the various constituencies involved. It will also identify effects of lay and expert concepts of detection limits and scope of biomonitoring surveillance on communication.

Summary

Given the central role of communication in the success of interpretation and use of biomonitoring data, but high uncertainty about what makes for effective biomonitoring communication, building infrastructure and research in this field must have high priority for biomonitoring funders and investigators. Without that priority, the whole field of biomonitoring could fail to advance.

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7

Research Agenda

INTRODUCTION

With the growth of biomonitoring to include more investigations, more chemicals, and expanded population sampling, the challenges of interpretation are increasingly evident. What does science tell the nursing mother when she learns that she has a large number of chemicals in her breast milk, all at relatively low concentrations? How should the findings of low concentrations of persistent chemicals in umbilical-cord blood be reported and interpreted? And, perhaps most important, what are the implications of biomonitoring results for public health and environmental policy? Those questions epitomize the challenges of biomonitoring with respect to its use, interpretation, and limitations, and the ethical and communication issues that it presents. This chapter provides a research agenda for addressing those issues to advance the application of biomonitoring.

In several instances, biomonitoring data have confirmed health effects of environmental exposures and have validated public-health policies. For example, population data on blood lead concentrations that were associated with adverse health effects provided the impetus for the U.S. Environmental Protection Agency (EPA) regulations reducing lead in gasoline. Methylmercury concentrations in blood and hair that were correlated with neurodevelopmental effects provided the rationale for EPA's revision of the oral reference dose. In those examples, the biomonitored concentrations of chemicals could be shown to be related to adverse health effects because of the body of epidemiologic, toxicologic, and clinical

data. In another example, data on serum cotinine, a biomarker of exposure to second-hand smoke, showed that serum cotinine in U.S. children and adults declined by more than 50% among nonsmokers from 1998 to 2002, demonstrating the effectiveness of smoking cessation efforts in the United States.

For population-based studies, biomonitoring data can help to identify chemicals that are found in the environment and in human tissues, can be used to monitor changes in exposure, and can be used to establish the distribution of exposure among the general population. Biomonitoring provides a measurement of exposure that—when used with available epidemiology, toxicology, and pharmacokinetic modeling data—can help to estimate how much has been absorbed into the body and estimate potential health risk. Biomonitoring can also be a very efficient means of assessing exposure and can provide a context for understanding environmental exposures on an international level.

In spite of the potential of biomonitoring, tremendous challenges surround its use. They include improving our ability to design biomontoring studies, interpreting what biomonitoring data mean for health risk and public health, addressing ethical uses of the data, and communicating results to policy-makers and the public.

To realize its potential, an investment in biomonitoring research is needed to address the critical knowledge gaps that hinder our ability to use and interpret the biomonitoring data. The committee's research recommendations focus not on specific chemicals but rather on methods that can be applied to a broad array of chemicals. Implementation of the research recommendations will benefit from enhancement of some parts of our nation's research infrastructure.

RESEARCH RECOMMENDATIONS

To address the challenge of improving the interpretation and use of biomonitoring data, the committee has developed four major findings and corresponding research recommendations. The committee considered these recommendations to be of the highest priority in advancing the field of biomonitoring. Addressing the knowledge gaps will require a broader vision of biomonitoring, including a coordinated scientific approach to setting priorities for biomarker development; better integration of epidemiology, toxicology, pharmacokinetic modeling, and exposure assessment to put biomonitoring results into a meaningful risk context; improved reporting of biomonitoring results; and understanding of the ethical issues that constrain the advancement of biomonitoring. Other research recommendations, not addressed below, are found in Chapters 3-6.

Priority Setting among Biomarkers for Development

Finding: There has not been a coordinated and consistent public-health-based strategy for selecting how chemicals are included in or excluded from biomonitoring studies. There is a need for a consistent rationale for selecting chemicals for study based on exposure and public-health concerns.

Recommendation: Develop a coordinated strategy for biomarker development and population biomonitoring based on the potential for population exposure and public-health concerns.

Biomonitoring offers great promise as an effective technique for identifying chemicals of potential public-health significance. The committee finds that broad population screening for a large number of chemical biomarkers has provided useful and at times surprising evidence of human exposure. That type of screening should continue. However, it can be improved. The current biomonitoring strategy relies on the emergence of biomarkers from various research avenues (such as epidemiology, analytic chemistry, and workplace monitoring), but the uncoordinated fashion in which this has occurred has allowed widespread exposures to go undetected for many years—for example, exposures to polybrominated diphenyl ethers (PBDEs) and perfluorooctanoic acid. In addition, susceptible subpopulations, including infants and children, are generally omitted from large-scale biomonitoring studies because of difficulty in sample collection.

The committee recommends that a coordinated scientific research strategy be developed to ensure that selection of chemicals for development of biomarkers and for biomonitoring focus, first and foremost, on the potential of chemicals to cause harm, and consider the likelihood of widespread exposure, including exposure of susceptible subpopulations. The biomonitoring-research strategy needs to set priorities among chemicals on the basis of one or more of the following: evidence of widespread exposure in the general population, biomonitoring data or exposure-analysis information that indicates exposure of susceptible subpopulations, toxicology data indicating that a chemical is capable of causing effects of public concern, and environmental persistence or use-pattern information that indicates that exposure will probably continue or increase in the future. The strategy should include a systematic analysis of chemicals to which there is widespread exposure so that priorities can be set for biomarker development. The biomarkers can be combined with biomarkers already developed via other avenues, such as epidemiologic research and workplace monitoring, to construct a comprehensive biomonitoring program.

Developing the coordinated scientific strategy will require input from various agencies involved in biomonitoring and supporting disciplines, in-

cluding the Centers for Disease Control and Prevention (CDC), EPA, the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), the Food and Drug Administration, and the U.S. Department of Agriculture. Coordinated input from those agencies would ensure that population-based biomonitoring studies would target chemicals of increasing public-health concern, with chemicals that are prudent to monitor for broad screening or status and trends purposes. The scientific strategy would need to be transparent to the public. Such a coordinated approach might eliminate redundancies in research efforts among agencies and help to leverage additional funds for the most pressing public-health questions.

In addition to developing a strategy for identifying specifically targeted chemicals, the committee recommends that population-based biomonitoring studies include a subset of samples to screen specific populations for untargeted analytes and to identify and quantify these chemicals. Such an approach is feasible with current analytic techniques that provide for the tentative identification of unknown analytes.

To address sensitive subpopulations better, including infants and children, the committee recommends the development of additional matrices—including cord blood, saliva, meconium, and breast milk—in concert with expanded analyses of infant blood or urine to enhance our ability to detect exposure during early life stages.

Developing Epidemiology, Toxicology, and Exposure-Assessment Research

Finding: Our ability to detect chemicals has outpaced our ability to interpret health risks. Epidemiologic, toxicologic, and exposure-assessment studies have not adequately incorporated biomonitoring for interpretation of health risks at the individual, community, and population levels.

Recommendation: Develop biomonitoring-based epidemiologic, toxicologic, and exposure-assessment investigations and public-health surveillance to interpret the risks posed by low-level exposure to environmental chemicals. Where possible, enhance existing exposure-assessment, epidemiologic, and toxicologic studies with biomonitoring to improve interpretation of results of such studies.

Our ability to interpret the risks associated with biomonitoring findings depends on our knowledge of exposure, toxicologic, pharmacokinetic, and epidemiologic data of particular chemicals, as illustrated by the framework in Table 3-1. To interpret biomonitoring data better in the context of

this framework and to understand the public-health implications of the data, coordinated research is needed to increase the use of biomonitoring in epidemiologic studies, to expand toxicologic studies to incorporate the collection of biomonitoring data and foster the development of pharmacokinetic models, and to incorporate exposure assessment in biomonitoring studies. Each is discussed below.

Development of the application of biomarkers in epidemiology is needed to improve the understanding of the relationships between biomonitoring data and health effects. As illustrated by our knowledge of blood lead that is based predominantly on epidemiologic studies that examined the relationship between blood lead and IQ in study subjects, epidemiologic studies may provide the optimal database for linking biomonitoring data to health effects. However, such information, as in the case of lead, is accumulated over many years and at high cost. The key question is when and how to use epidemiology more efficiently to attain such understanding of other chemicals.

Quantitative epidemiologic research is expensive, but the emphasis should be on cost effectiveness, not on cost. The most scientifically desirable scenario is the funding of a major epidemiologic study specifically targeted at interpreting biomonitoring data; however, funding realities limit the feasibility of that. The federal budget for epidemiology related to chemical exposures is significant and should be further leveraged. Almost all epidemiologic studies have some metric of exposure (such as questionnaires, environmental measurements, and biomonitoring), and each approach has different degrees of value and cost. With careful attention to study design, supplemental funding for planned or impending epidemiologic studies that take tissue samples and analyze them for biomarkers could contribute substantially to interpretation of the data and assist in our understanding of the data gaps in the continuum from exposure to disease.

Consideration should be given to increasing the number of biosamples collected and stored in epidemiologic studies to provide future research opportunities for assessing associations between biomarkers and outcomes within existing study designs. Examples include recent analyses of organochlorine in biologic samples collected and stored decades earlier as part of the 1959-1965 National Collaborative Perinatal Project (Borrell et al. 2004; Gray et al. 2005; Longnecker et al. 2005). As new biomonitoring results have become available, spinoff studies have been initiated within the NIEHS-EPA Center for Children's Environmental Health, for example, to evaluate effects of prenatal phthalate and PBDE exposures by using banked samples within the existing research designs (Eskenazi et al. 2005). The National Children's Study (NCS), whose funding is currently being debated, has the potential to offer many opportunities to assess relationships

between high-priority biomarkers and health outcomes, both prospectively and retrospectively. The committee also recognizes that population-based biomonitoring studies complement the national strategy of public-health tracking and the links between environmental exposures and public health. The applications of biomonitoring in those studies are important examples for future epidemiologic investigations.

Toxicologic studies need to be expanded to incorporate collection of biomonitoring data in animals that can be related to humans. Much of the dose-response information used in risk assessments is derived from animal toxicologic studies, and these do not collect information on internal dose. Therefore, dose-response relationships can be expressed only in terms of external dose (such as milligrams per kilogram per day). However, to interpret biomonitoring data, the relationship between internal dose (biomarker concentration) and effect must be understood.

Expansion of animal toxicologic study designs to include collection of biomarker data (for example, concentrations of the parent chemical in blood or of key metabolites in urine) will facilitate the development of biomarker-response relationships that can be extrapolated across species to interpret human biomonitoring results. That involves adding pharmacokinetic groups to a toxicologic study design or recreating a toxicologic study (with identical species and dose groups) that provided key dose-response information. Ideally, sufficient pharmacokinetic data will be collected from the study to facilitate the development of a physiologically based pharmacokinetic (PBPK) model that can be used to predict biomarker concentrations in animals across a wide range of doses and whose results may be extrapolated to humans. For example, NTP toxicologic protocols have added a pharmacokinetic component that has the potential to assist in the development of PBPK models and estimation of biomarker concentrations in toxicologic studies (Buchanan et al. 1997).

The incorporation of biomonitoring data in toxicologic studies will maximize their utility for interpreting biomonitoring data. Characterizing a biomarker-response relationship in animals could lead to development of reference doses or cancer slope factors based on biomarker concentration rather than external dose. Biomarker-based toxicity values would be directly applicable to interpreting human biomonitoring studies. Fostering development of PBPK models that can be used for internal dose reconstruction in critical toxicologic studies will facilitate extrapolations across species, dose routes, and doses.

Exposure assessment should be a component of population-based biomonitoring studies to facilitate interpretation of the data. Typically, large-scale biomonitoring studies do not evaluate potential sources of exposure. That often leads to the question, Where is the exposure coming from? For some chemicals, exposure pathways may be well defined from previous

studies (for example, mercury in the general population comes primarily from fish ingestion); for others, however, it may be largely unknown.

The committee recommends the inclusion of a detailed and accurate exposure analysis for a subset of the biomonitored population in large-scale biomonitoring studies that includes analyses of environmental media in the residence and uses a survey instrument to obtain information on diet, consumer product use, occupational exposures, and other factors relevant to the chemical exposure pathways that are being examined. The exposure assessment can be patterned on protocols used in other exposure analyses, such as the National Human Exposure Assessment Survey (NHEXAS), the Minnesota Children's Pesticide Exposure Study, and Children's Total Exposure to Pesticides and Other Persistent Organic Pollutants.

In addition, existing databases where environmental media and biomonitoring data are collected (such as NHEXAS) could be further studied to estimate exposure and explore the relationships between biomarker concentration and exposure. That information can be used to apportion chemical intake into the different exposure pathways to assist in interpreting population variability, to calculate exposure by combining environmental measurements with survey information to verify estimates of exposure from pharmacokinetic models, and to identify research needs on the basis of discrepancies between estimates obtained from the exposure-pathways analysis and biomonitoring results.

Several other kinds of research would enhance our interpretation of the biomonitoring data. Such research includes understanding and characterizing the effect of human variability on biomonitoring results, including sampling time and population variability in metabolism, creatinine clearance, and other pharmacokinetic factors influenced by age and sex. Specific research includes dose-simulation modeling techniques that combine behavioral and pharmacokinetic factors to characterize how population variability in exposure can affect biomonitoring results in different age groups (Zartarian et al. 2000; Rigas et al. 2001) and the development of pharmacokinetic models for various susceptible subpopulations to predict biomonitoring results.

The committee recommends that efforts be made to develop human pharmacokinetic models early in the study-design process to understand the influence of such factors as metabolism, sampling time, and population variability, that are critical to interpretation of the biomonitoring data.

Evaluating the extent of exposure to mixtures and developing methods to assess public-health effects by using emerging technologies (such as -omics) are important research needs. Because population-based biomonitoring studies report on human exposures to a large number of chemicals, understanding exposures to mixtures is critical. Monte Carlo simulation modeling techniques are needed to estimate the number and concentrations

of chemicals to which the population in the CDC biomonitoring study is exposed. Animal bioassays should be developed to assess the combined effects of chemical mixtures that are commonly found in human tissues (e.g., NTP 1993a; NTP 1993b; Yang 1994). In addition, modeling techniques need to be developed to simulate the pharmacokinetic and pharmacodynamic interactions of multiple chemicals (Poulin et al. 2001; Poulin and Theil 2002; van de Waterbeemd and Gifford 2003; Yang et al. 2004; Reddy et al. 2005; Yang et al. 2005; Yang et al., unpublished material, 2006).

Emerging technologies, including toxicogenomics, can be used to develop methods to assess public-health effects better. For instance, toxicogenomics provides an opportunity to move beyond the traditional approaches of exposure assessment—based on one exposure to one chemical in one environmental medium—to an approach involving multiple exposures and via multiple biologic-response pathways (Weis et al. 2005; Wild 2005). A recent molecular epidemiologic study by Vermeulen et al. (2005) that used array-based proteomics to develop potential biomarkers of exposure and early biologic effect demonstrated the potential for -omics biomonitoring in chemical-exposed populations. Emerging technologies will also allow for the intergration of biomarkers of exposure with those of effect to determine whether the markers of effect track with individual chemicals or with exposure to mixtures.

Reporting Results of Biomonitoring Studies

Finding: Effective communication of results is among the biggest challenges to the future of biomonitoring. Without appropriate strategies for understanding the communication issues needed in the design, implementation, and evaluation of biomonitoring studies, our power to interpret and use the resulting data effectively is hampered.

Recommendation: Advance individual, community, and population-based strategies for reporting results of biomonitoring studies.

Given the central role of communication in interpreting and using biomonitoring data, developing research must have high priority for biomonitoring investigators and funders. To that end, the committee proposes three communication research recommendations (detailed in Chapter 6). Understanding how laypeople and scientists conceive of the causal links between external dose, biomarker concentrations, and biologic effects and their views about exposure reduction and risk managers, will reveal their agreements and disagreements and will suggest bases of messages that could reduce disagreements. Assessing the content of current biomonitoring education and com-

munication materials will help to evaluate their efficacy, and determine the extent to which beliefs about causal linkages are accurately reflected in them. Alternative messages about biomonitoring, especially those concerning the deep uncertainties in the field, should be informed by research on people's beliefs and on how people communicate. Testing responses to alternative messages on individual, community, and population-based aspects of biomonitoring will advance communication strategies.

Addressing Ethical Issues

Finding: Biomonitoring research presents a number of bioethical concerns about informed consent and the interpretation of results. Much of biomonitoring research is conducted with anonymized samples that limit the communication of results and potential followup with study subjects.

Recommendation: There is a need for review of the bioethical issues confronting the future of biomonitoring, including confidentiality, informed consent, reporting of results, and public health or clinical followup.

Participants in public-health studies that measure hundreds of biomarkers might give "informed consent" only with respect to the general objectives of the study on the grounds that detailed discussion of each biomarker is prohibitive. However, failing to make available more detailed information, no matter how many chemicals are involved in a study, raises ethical questions.

Because of the challenges posed by informed consent for studies that use high-output, high-throughput technologies, the committee recommends research that develops, evaluates, and disseminates methods that ethically and practically inform study subjects during recruitment and during later communication of study results.

There is a concern that blanket consent (for example, for future testing of tissue samples with genomic or metabonomic assays that are not available at the time of study recruitment) has the potential to result in abuse. It is a highly contentious issue and particularly pertinent to sample collection from children and other susceptible subpopulations. As a result, it has led to increased difficulty in obtaining institutional review board approval for some kinds of biomonitoring studies.

The committee is sympathetic to such concerns but is also aware of the ethical (and practical) problems of undue replication of tissue sampling that the implicit ban forces, as each new sample application is imagined. Therefore, the committee recommends that research be conducted to develop new approaches for obtaining consent for future uses of biomonitoring data.

INFRASTRUCTURE NEEDS TO IMPLEMENT RESEARCH AGENDA

The current infrastructure to support research recommendations discussed previously is severely limited. Improvements in the research-related infrastructure are needed to support these recommendations and to enhance the value of the biomonitoring activities described in preceding chapters. In many cases, the recommendations for infrastructure needs are cost-effective in that they rely on expansion of structures and activities that are already in place. The infrastructure needs encompass laboratory issues, expanding the scope and utility of CDC's National Health and Nutrition Examination Surveys (NHANES) data, maximizing the utility of collected human samples, and fostering international biomonitoring collaboration.

Laboratory Issues

Further investments in federal, state, and university laboratories are needed to create the national capacity to exploit biomonitoring fully as a public-health tool. Analysis of human specimens for trace concentrations of environmental chemicals poses serious challenges to the analytic chemistry laboratory. Specimen sizes are often small, the required detection limit is often low, and many interferences are typically present in a complex matrix, such as blood or urine. The recent growth in biomonitoring applications has been made possible by commercial availability of a new generation of more sensitive and selective instrumentation for chemical identification and quantification, of isotopically labeled internal standards, and of robotic systems capable of automated sample preparation. The costs associated with those items and the specialized skills needed to perform the tests have limited the number of laboratories capable of biomonitoring measurements. In recognition of the national deficiencies in the biomonitoring-laboratory capacity, CDC funded 33 states to identify local public-health problems and to develop plans to create the biomonitoring-laboratory capacity needed to address them. Because of fiscal constraints, only three grants to provide the needed laboratory capacity were ultimately awarded—and at substantially decreased funding levels (APHL 2006; CDC 2005). Funds should be appropriated to expand CDC support of state public-health laboratories and to allow implementation of their already-developed plans to address local exposure-related problems.

Improvement in the array of chemicals capable of being measured in human specimens is needed. For example, the Government Accountability Office (GAO, previously the General Accounting Office) assembled a non-exhaustive list of 1,456 chemicals considered by the Department of Health and Human Services, EPA, or other federal entities to pose a threat to human health (GAO 2000). Laboratory methods have not been developed and validated to measure most of them. The recent NHANES report, which provided

the most extensive biomonitoring survey of the U.S. population available, lists only 148 analytes, reflecting a partial representation of potential exposures, many of which are not discretely listed in the GAO report.

Laboratory methods in use today need further improvement. Lower detection limits will facilitate studies of background contamination in "unexposed" populations and determination of reference ranges. Many analytes cannot now be conveniently measured in a large proportion of such people. For example, the 95th percentile lipid-adjusted serum 2,3,7,8-TCDD concentrations were below the limits of detection for all seven population groups tabulated in the most recent NHANES report (CDC 2005). Even when censored data are less predominant, they force assumptions about the distribution of results below the detection limit, and this introduces uncertainty into many statistical calculations and complicates efforts to detect temporal, geographic, or ethnic differences in exposure (Needham 2005). Greater analytic sensitivity can also allow testing of smaller sample aliquots. Smaller aliquots will permit more tests on a single sample, help to identify more clearly chemical exposures that correlate with one another, and help to identify exposure sources.

Laboratories must develop the ability to test specimen types and sample volumes that can be collected with less invasive sampling techniques to facilitate subject participation, especially in studies involving children. More sensitive analytic methods can allow collection of smaller specimens; this is especially important in studies involving newborns and children (Barr et al. 2005). Additional analytic methods must be developed and validated to address specimens less invasively obtained (such as saliva, exhaled breath, and breast milk).

The need for high-throughput, low-cost testing procedures will be increasingly apparent as biomonitoring techniques are more widely applied to large-scale epidemiologic studies; mass-casualty events, such as chemical terrorism and chemical accidents; and efforts to define reference ranges in multiple but narrower segments of the population. Substantial throughput and cost improvements may require innovative approaches quite different from those in use today.

Improving the quality of biomonitoring-laboratory data (especially their accuracy, precision, and interlaboratory comparability) will be important for many of the applications discussed in Chapter 3 and for supporting the research recommendations described previously. The committee recommends that a group of biomonitoring-laboratory experts be assembled to make consensus recommendations to improve the quality of data used for medical and research purposes. The Clinical and Laboratory Standards Institute (CLSI 2006) exemplifies an organization that might be charged with this task. Possible goals include

- Creating consensus recommendations for good laboratory practices associated with clinical-sample analysis for environmental and occupational medicine.
- Making recommendations to increase the availability of isotopically labeled analogues of target chemicals, such as taking advantage of the extensive use of labeled chemicals in CDC's analytic program.[1]
- Developing a plan to increase the available array of biomonitoring-relevant analytic reference materials (human samples containing chemicals at known concentrations appropriate for environmental or occupational medicine); the National Institute of Standards and Technology's Standard Reference Material Program is a useful model of such an activity.
- Developing a mechanism to expand interlaboratory comparison programs to include a broader array of chemical targets in human specimens; no broadly based program exists in the United States.
- Improving the quality of the biomonitoring laboratories that analyze human samples for the purposes of diagnosis, prevention, treatment, or health assessment. These laboratories are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (42 CFR 493 [2000]). However, the focus of this statute is mainstream clinical testing. For example, the 41-page CLIA tabulation of approved proficiency-test providers lists only one environmental chemical (blood lead) (CMS 2005).

The proposed consensus committee should consider whether the CLIA program should become more active in ensuring the quality of environmental and occupational biomonitoring data by, for example, establishing a chemistry subspecialty in environmental and occupational medicine or expanding the array of biomonitoring-relevant proficiency tests available from the Center for Medicare and Medicaid Services-approved providers.

Expanding the Scope and Utility of NHANES Data

As noted in Chapter 2, NHANES and the associated *National Report on Human Exposure to Environmental Chemicals* provide the most comprehensive summary of biomonitoring data on a representative sample of

[1]Since much of the cost incurred in custom synthesis is independent of the quantity prepared, supporting CDC to contract for the synthesis of larger quantities of labeled compounds than required for its own purposes and making them available to the biomonitoring laboratory community could be cost-effective. Greater availability of these materials is essential if the more robust isotope dilution methods are to find wider applicability. In particular, the comparability of data sets generated by different laboratories will be improved if a common labeled standard is used.

the U.S. population. The committee concurs with CDC that the current effort provides data essential for identifying chemicals and concentrations, establishing reference ranges, tracking temporal exposure trends, assessing the effectiveness of interventions to reduce exposure, and setting priorities for research on human health effects (CDC 2005). The achievements of NHANES argue for its expansion and for procedural changes that will enhance the utility of the resulting data.

NHANES reports results by age group, sex, and racial group (Mexican American, non-Hispanic black, and non-Hispanic white). The dataset is insufficient to address other ethnic groups or to determine exposures by locality, state, or region. The committee considers that the missing data are important for setting priorities among groups and geographic areas for intervention, and obtaining them may lead to an improved understanding of exposure pathways. Additional ethnic groups and susceptible subpopulations might be incorporated by program expansion or oversampling within the NHANES program design. Production of location-specific data, especially if temporal trends are sought, may require substantial program redesign, because samples are now collected only from a small number of sites each year (Schober 2005). Alternatively, such data could be produced by supporting state- or city-based health and nutrition examination survey (HANES) projects. The New York City HANES project is a useful example of such a program (Gwynn and Thorpe 2004).

CDC staff have noted that NHANES collects only a small amount of biomonitoring data relevant to exposures in the fetus, infant, toddler, and preschooler (Needham 2005). The committee recognizes that constraints intrinsic to the existing NHANES protocol may make addressing those groups difficult and therefore recommends continued and expanded federal support of the NCS (NCS 2005).

The committee noted that the data presented in the printed *Third National Report on Human Exposure to Environmental Chemicals* are incomplete and that the content of the larger dataset available on the CDC Web site (NCHS 2005) is not optimized to benefit the entire scientific and medical community. For example, the report's tables and charts do not include data below the 50th percentile. The publicly available dataset should be sortable by sample type, chemical, region or location, age group, race, and socioeconomic status to facilitate interpretation and identification of groups at higher risk. Some applications of the dataset, such as analysis of exposure to mixtures and chemical interactions, require knowledge of the pattern of chemicals present in individual subjects. CDC should endeavor, where sample volumes permit, to perform the broadest array of tests possible on each subject to maximize the opportunity to detect correlations among chemicals measured in different analyses.

Maximizing the Utility of Collected Human Samples

Chapter 4 outlines the steps associated with designing and executing a biomonitoring study. The costs associated with assembling and characterizing a population for study, securing informed consent, and collecting human specimens are substantial. Properly collected and stored specimens remain valuable after completion of the initial study, especially if informed consent was or can be obtained for future studies. When already collected and characterized samples are available, costs of future studies are decreased; samples are readily available for pilot studies, for laboratory-method validation, and for testing with newly developed biomarkers (Holland et al. 2005). For some applications (such as tracking time trends of exposure), specimen banks are essential. The committee considers that future progress toward the research goals described in this chapter will be accelerated and study costs lessened by the increased availability of already collected and characterized samples. However, the difficulties associated with long-term sample storage are substantial. Each sample needs readily accessible, but secure, records related to chain of custody, processing, location, and temperature stability. Costs of equipment (for example, freezers, cryotanks, automated sample handling and tracking equipment and software, and back-up power supplies), space costs, and personnel costs can be high. The committee therefore recommends expanded long-term funding for existing biorepositories and the creation of new biorepositories for support of biomonitoring studies.

Fostering International Biomonitoring Collaboration

Because biomonitoring is conducted on an international level by numerous organizations and there is much knowledge to be gained from understanding worldwide patterns of exposure, the committee encourages the global exchange of biomonitoring information and expertise. That would include sharing of biomonitoring data, study approaches, and tracking of trends. To that end, the committee encourages the development of such information exchanges between EPA and the Organisation for Economic Co-operation and Development (OECD).

SUMMARY

This chapter presents the major research recommendations required to improve the use and interpretation of biomonitoring data for improving public health. Implementation of the research recommendations will require expansion of the biomonitoring infrastructure. Table 7-1 summarizes the committee's research recommendations and infrastructure needs.

TABLE 7-1 Summary of Major Points in Research Agenda

Research Recommendations
1. Develop a coordinated strategy for biomarker development and population biomonitoring based on the potential for population exposure and public-health concerns.
2. Develop biomonitoring-based epidemiologic, toxicologic, exposure-assessment, and public-health surveillance to interpret the effects of low-level exposure to environmental chemicals. Where possible, enhance existing exposure-assessment, epidemiologic, and toxicologic studies with biomonitoring to improve interpretation of continuing studies.
a. Increase use of biomarkers in epidemiology to improve the understanding of relationships between biomonitoring data and health effects.
b. Expand toxicologic studies to incorporate collection of biomonitoring data on animals that can be related to human biomonitoring results.
c. Incorporate exposure assessment as a component of population-based biomonitoring studies to facilitate interpretation of data.
d. Develop human pharmacokinetic models early in the study-design process to understand the influence of such factors as metabolism and sampling time that are critical for interpretation of the data.
3. Advance individual, community, and population-based strategies for reporting results of biomonitoring studies.
a. Understand how scientists and nonscientists conceive of the causal links between external dose, biomarker concentrations, and biologic effects.
b. Assess the content of biomonitoring education and communication materials to evaluate their efficacy.
c. Conduct research on people's views and on how people communicate about uncertainty in the biomonitoring field.
4. Study and address ethical issues that constrain advancement of biomonitoring and that limit information available to study participants.
Infrastructure Needs to Support Research Agenda
1. Increase laboratory capacity and capability.
a. Provide additional investments in federal, state, and university laboratories to create the national capacity to exploit biomonitoring fully as a public-health tool.
b. Improve laboratory methods including ability to measure a greater number of chemicals, analytic sensitivity, quality of data, and development of analytic methods that use less invasively obtainable specimens.
2. Expand scope and utility of CDC NHANES data.
a. Collect additional data on ethnic groups, specific locations, and sensitive subpopulations, including fetus, infant, toddler, and preschooler.
b. Report additional results in the printed version of the national exposure reports (for example, below the 50th percentile) and ensure that the publicly available dataset is sortable by sample type, chemical, location, and socioeconomic characteristics.
3. Increase the availability of already collected and characterized samples and expand long-term funding for existing biorepositories and new biorepositories for supporting biomonitoring studies.
4. Encourage the development of international collaborations between EPA and OECD for global sharing of biomonitoring information and expertise, including data, study approaches, and tracking of trends.

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Appendix A

Biographic Information on the Committee on Human Biomonitoring for Environmental Toxicants

Thomas A. Burke (*Chair*) is professor and associate chair of the Department of Health Policy and Management at the Johns Hopkins University Bloomberg School of Public Health, with joint appointments in the Department of Environmental Health Sciences and the School of Medicine's Department of Oncology. He is also founding codirector of the university's Risk Sciences and Public Policy Institute. At Johns Hopkins, he was principal investigator for the Pew Environmental Health Commission; this research developed the recommendations for the Centers for Diseases Control and Prevention (CDC) National Environmental Public Health Tracking Network. He received his PhD in epidemiology from the University of Pennsylvania and his MPH from the University of Texas. Before joining the university, Dr. Burke was deputy commissioner of health for the state of New Jersey and director of science and research for the New Jersey Department of Environmental Protection. In New Jersey, he directed initiatives that influenced the development of national programs, such as Superfund, the Safe Drinking Water Act, and the Toxics Release Inventory. His research interests include environmental epidemiology and surveillance, the evaluation of community exposures to environmental pollutants, the assessment and communication of environmental risks, and the application of epidemiology and health risk assessment to public policy. Dr. Burke was the inaugural chair of the advisory board to the director of the CDC National Center for Environmental Health and is a member of the National Research Council Board on Environmental Studies and Toxicology. He has served on several other National Research Council committees; he was a

member of the Committee on the Toxicological Effects of Methyl Mercury and chair of the Committee on Toxicants and Pathogens in Biosolids Applied to Land. In 2003, he was designated a lifetime national associate of the National Academies

Mark Cullen is professor of medicine and public health at Yale University School of Medicine. His research interests are in occupational and environmental medicine, including isocyanate exposure in automobile-shop workers, lung cancer in people exposed to asbestos, and lead toxicity in workers. He has published several textbooks, including *Clinical Occupational Medicine* and *Textbook of Clinical Occupational and Environmental Medicine*. Dr. Cullen received his MD from Yale University and did his residency in internal medicine. He is a member of the DuPont Epidemiology Review Board, a member of the MacArthur Foundation Network on Socioeconomic Status and Health, and a corporate medical director for the Aluminum Company of America. Dr. Cullen is a member of the Institute of Medicine and served as a member of its Board on Health Sciences.

George Eadon is director of the Division of Environmental Disease Prevention of the New York State Department of Health and associate professor in the Department of Environmental Health Sciences at the State University of New York, Albany. He is actively engaged in a number of biomonitoring studies being conducted by the state of New York. Dr. Eadon has served as assistant and associate professor of chemistry and later as chairman of the Department of Environmental Health Science and Toxicology at the State University of New York, Albany. Dr. Eadon received his PhD in chemistry from Stanford University. He serves on the advisory board of New York's Environmental Public Health Tracking Grant.

Peter Farmer is an honorary professor in the Department of Biochemistry and Cancer Studies and Molecular Medicine and a joint director of the Cancer Biomarkers and Prevention Group at the University of Leicester, UK. His research group studies the molecular action of carcinogenic and other toxic chemicals and develops biomarkers of exposure and effects. The group is involved in several international collaborations aimed at developing methods for monitoring human exposure to environmental and occupational genotoxic chemicals. One of the major focuses of Dr. Farmer's research is the in vivo interaction (adduct formation) of environmental chemicals, or their active metabolites, with protein and DNA. He received his DPhil in chemistry from Oxford University. He is the chairman of the Committee on Mutagenicity of Chemicals in Food, Consumer Products, and the Environment of the UK Department of Health. He is also a member of the Health Effects Institute Research Committee.

Gary Ginsberg is a senior toxicologist in the Division of Environmental Epidemiology of the Connecticut Department of Public Health. In addition, he is an assistant clinical professor at the University of Connecticut School of Medicine and an adjunct faculty member of the Yale University School of Medicine. Dr. Ginsberg is involved in the use of toxicology and risk-assessment principles to evaluate human exposures to chemicals in air, water, soil, food, and the workplace. He provides risk-assessment expertise to the department and other state agencies in standard-setting and site-remediation projects. He received his PhD in toxicology from the University of Connecticut. Dr. Ginsberg is a member of the Federal Advisory Committee on Children's Health Protection, which reports to the administrator of the Environmental Protection Agency.

Carol J. Henry serves as vice president for science and research at the American Chemistry Council (ACC) and is responsible for the management and guidance of the Long-range Research Initiative. She received her PhD in microbiology from the University of Pittsburgh. Before joining the ACC, Dr. Henry served as director of the Health and Environmental Sciences Department of the American Petroleum Institute. Earlier she completed 5 years of public service, serving as associate deputy assistant secretary for science and risk policy at the U.S. Department of Energy and as director of the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency. Before the latter appointment, she was executive director of the International Life Sciences Institute's Risk Science Institute. A diplomate of the American Board of Toxicology, Dr. Henry is a member of the Society of Toxicology and the American College of Toxicology, of which she has been president. She served on the Board of Scientific Counselors of the National Toxicology Program and the Environmental Protection Agency (EPA) Clean Air Act Science Advisory Committee's Blue Ribbon Panel on Oxygenates in Gasoline. Dr. Henry recently completed two terms as a member of the National Research Council Board on Environmental Studies and Toxicology and as a member of the Committee to Review EPA's Research Grants Program. She serves on the Board of Directors of the CIIT Centers for Health Research; the Roundtable for Environmental Health, Medicine and Science of the Institute of Medicine; and the Chemical Sciences Roundtable of the National Research Council.

Nina Holland is an associate adjunct professor of genetics and toxicology and director of the biorepository at the University of California, Berkeley School of Public Health. Her scientific interests include molecular epidemiology of children's health, cytogenetics, and reproductive toxicology. In Dr. Holland's Laboratory of Children's Environmental Health, research focuses on the development and implementation of genetic and immuno-

logic biomarkers in children's studies. Dr. Holland received her PhD in genetics from the Institute of Molecular Biology and Genetics of the Academy of Sciences of Ukraine. She served as a director of the Laboratory Cores of the Superfund Center and the Center for Children's Environmental Health at the University of California, Berkeley. Dr. Holland is a member of the coordinating committee on the International Project on Micronucleus Studies in Humans. She has organized several sessions on molecular epidemiology of children's environmental health at national and international meetings.

Gunnar Johanson is professor of occupational toxicology and risk assessment and director of the Division of Work Environment Toxicology at the Institute of Environmental Medicine of the Karolinska Institutet, Sweden. His research focuses on the study of toxicokinetics of chemicals after controlled exposure of volunteers and on the development of physiologically based pharmacokinetic models. Dr. Johanson received his PhD in toxicology from the Karolinska Institutet. He is a member of the Scientific Committee on Occupational Exposure Limits of the European Commission, chairman of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals, and vice chairman of the Swedish Criteria Group for Occupational Exposure Limits. In 2001, Dr. Johanson was a recipient of the Herbert E. Stokinger Award for outstanding achievement in industrial toxicology from the American Conference of Governmental Industrial Hygienists.

Branden Johnson is a research scientist with the Bureau of Environmental Health Science and Environmental Assessment in the Division of Science, Research, and Technology of the New Jersey Department of Environmental Protection (NJDEP). His research focuses on risk communication and risk perception regarding environmental hazards. He holds several adjunct and visiting professorship positions at Rutgers University, in the School of Public Health and in the Departments of Human Ecology and Geography. Before joining NJDEP, Dr. Johnson was associate professor of science, technology and society at Michigan Technological University. He was chair of the Risk Communication Specialty group, and President of the Philadelphia Chapter of the Society for Risk Analysis, and is currently President of the Risk Assessment and Policy Association. Dr. Johnson received his PhD in geography from Clark University. Dr. Johnson served as a member of the National Research Council Committee on Drinking Water Contaminants.

Dorothy E. Patton is an adjunct professor at the Georgetown (University) Public Policy Institute and a consultant with the Risk Science Institute of the International Life Sciences Institute. Before retiring in July 2000, Dr.

Patton's 24-year tenure with the U.S. Environmental Protection Agency included positions as Director of the Office of Science Policy, Executive Director of the Science Policy Council and Executive Director of the Risk Assessment Forum. In these positions, her responsibilities included developing and implementing risk assessment policies and practices, environmental research planning and prioritization, and long-range strategic planning in line with congressional mandates. She began her EPA career as an attorney in EPA's Office of General Counsel, where she worked on air, pesticides, and toxic substances issues. She holds a B.S. in chemistry from the University of Wisconsin, a Ph.D. in biology from the University of Chicago, and a J.D. from Columbia University School of Law. Her teaching experience includes an assistant professorship (biology) at York College of the City University of New York, as well as seminars and training workshops for risk assessment professionals.

Gerald van Belle holds joint appointments as professor in the Departments of Biostatistics and of Environmental and Occupational Health Sciences at the University of Washington. Dr. van Belle received his PhD in mathematical statistics from the University of Toronto. His research has focused on the use of statistics to study various environmental health issues, including exposure to pollutants in air and drinking water, and environmental risk factors for Alzheimer's disease. Dr. van Belle served as a member of the National Research Council Board on Environmental Studies and Toxicology and was a member of the Committee to Review EPA's Research Grants Program.

Claude Viau is professor in the Department of Environmental and Occupational Health at the University of Montreal; from 1994 to 2002, he served as chairman of the department. He was also senior risk management advisor of the Healthy Environment and Consumer Safety Branch, Health Canada from November 2004 to January 2006. Dr. Viau has conducted numerous analytic chemistry, toxicology, and biomonitoring studies. His current research focuses on biomonitoring of polycyclic aromatic hydrocarbon exposure, percutaneous penetration of chemicals, and styrene neurotoxicity. He received his MSc in analytic chemistry from the University of Montreal and his PhD in industrial toxicology from the Université de Louvain (Bruxelles). Dr. Viau is a member of the American Conference of Governmental Industrial Hygienists Biomonitoring Exposure Indices Committee and serves as president of the Scientific Committee on Occupational Toxicology of the International Commission on Occupational Health.

Robin Whyatt is deputy director of the Columbia Center for Children's Environmental Health and associate professor in the Department of Envi-

ronmental Health Sciences at the Mailman School of Public Health. Dr. Whyatt's research focuses on the effects of environmental exposures of women and children, including the developing fetus. She received her Dr.P.H. from the Mailman School of Public Health. Before going to Columbia University, she was a senior staff scientist at the Natural Resources Defense Council. Dr. Whyatt has published widely on the application of biologic markers to studies of environmental risks in infants and children and on the effects of environmental exposures during fetal development. She is a member of the Science Advisory Board of the Cincinnati Children's Environmental Health Center and is cochair of the Chemical Exposure Workgroup of the National Children's Study.

Raymond Yang is professor of toxicology and cancer biology at the Colorado State University. Dr. Yang's research focuses on the toxicology of chemical mixtures and biologically based computer modeling. He received his PhD in toxicology and entomology from the North Carolina State University. Dr. Yang is the editor or coeditor of two books: *Toxicology of Chemical Mixtures: Cases Studies, Mechanisms, and Novel Approaches* and *Physiologically Based Pharmacokinetics: Science and Applications*. Dr. Yang serves on the Board of Scientific Counselors of the National Center for Environmental Health and Agency for Toxic Substances and Disease Registry of the Centers for Disease Control and Prevention and serves on the Pacific Northwest National Laboratory Environmental Technology Directorate Review Committee. He was a member of the Institute of Medicine Committee on Interactions of Drugs, Biologics, and Chemicals in Deployed U.S. Military Forces and a member of the National Research Council Subcommittee on Mixtures.

Appendix B

Additional Case Studies Used to Exemplify Interpretative Approaches Described in Chapter 5

ADDITIONAL CASE STUDIES

Chapter 5 describes a variety of approaches for interpreting biomonitoring results, ranging from direct application of biomarker-response relationships found in epidemiologic studies to physiologically based pharmokinetic (PBPK) modeling based on animal data. Although Chapter 5 provides several chemical examples of the approaches described, the additional case studies discussed in this appendix are useful to illustrate the data needs and limitations.

Limitations and Potential Utility of Biological Exposure Indices for Interpreting Biomonitoring Results: Styrene

Chapter 5 described general limitations of extrapolating workplace biomarker indices, such as Biological Exposure Indices (BEIs) to the general public. However, biomarker-exposure dose relationships established in the workplace may have utility for developing pharmacokinetic models that could be used to interpret biomonitoring data on the general public.

The chlorpyrifos and phthalate examples demonstrate that urinary biomarker data can be used within the context of pharmacokinetic modeling to interpret human exposure and risk. For a number of workplace urinary biomarkers, simple approaches have been used to relate biomarker concentration to exposure dose. A prime example is styrene: an empirically derived relationship between urinary concentration of the metabolite, man-

delic acid, and the workplace air concentration has been developed (ACGIH 1991). A commonly used BEI for styrene is based on that urinary measure. Different equations are available to convert urinary concentration from milligrams per liter of urine or from milligrams per gram of creatinine back to a time-weighted average inhaled concentration. The urinary biomarker has been used to test correlations between styrene exposure and adverse effects in worker populations with respect to sperm DNA abnormalities, neurologic effects, and renal effects (Lindstrom et al. 1976a,b; Harkonen 1977; Vyskocil et al. 1989; Migliore et al. 2002).

The empirical relationship between urinary biomarker and ambient concentration has utility for screening worker populations, but less utility for risk assessment in the general population. The equations are valid only if urine is collected after an 8-hour workshift. Furthermore, the relationship between amount in urine and air concentration will depend on level of exertion and respiratory rate, which may differ between the workplace and the general population. Those limitations will generally occur with any occupation-based algorithm for relating urinary biomonitoring results to air concentration or exposure dose. However, such empirical data can be used to calibrate pharmacokinetic models that can take into account exposure and physiologic variables and thus can be applicable to both the workplace and the general population. The example described elsewhere for the chlorpyrifos metabolite is a case in point.

Regarding styrene, the variety of controlled human oral and inhalation studies that relate dose to urinary concentration and the existence of a pharmacokinetic model (Droz and Guillemin 1983) could facilitate interpretation of mandelic acid concentration in urine. A caveat in this regard is that other chemical exposures can produce mandelic acid in urine, such as ethyl benzene, acetophenone, and phenylglycine (ACGIH 1991). Those "background" sources would be more likely to confound low-level general-population biomarker results than workplace end-of-shift results.

It is noteworthy that the styrene reference concentration (RfC) in the Integrated Risk Information System is based on the biomarker-response relationship found in workers (Mutti et al. 1984; EPA 1998). The Environmental Protection Agency (EPA) used the relationship of urinary biomarker to ambient-air concentration of workers to develop an RfC that was adjusted for the difference in exposure time between the workplace and the general population. That is a valid approach because it derives a workplace concentration-toxicity relationship in workers, which can then be adjusted for the general population to account for differences in exposure time and can take uncertainty factors into account. It is different from direct adjustment of the styrene BEI to evaluate human population biomonitoring data on styrene metabolites in urine, which would have the uncertainties described above and in Chapter 5.

Case Example of Biomonitoring-Results Interpretation Based on Biomarker-Effect Relationship Developed in Epidemiologic Studies: Methylmercury

In addition to the lead example presented in Chapter 5, the work done with methylmercury is an important illustration of the great utility of biomarker-effects data from human studies. The EPA's risk assessment of methylmercury is based on such data generated in prospective epidemiologic research on effects of in utero exposure and adverse postnatal neuropsychologic sequelae (NRC 2000; Rice et al. 2003). Two biomarkers were used in the risk assessment: mercury in maternal hair collected at delivery and mercury in umbilical cord blood. Both biomarkers appear to be reliable internal dosimeters for exposure to methylmercury during pregnancy. The mercury biomarker in hair and blood is total mercury, including inorganic and organic forms. For the most part, that biomarker represents methylmercury from fish consumption in that this is the major source of systemically absorbed mercury. Total mercury in hair constitutes a relevant dosimeter in that it indicates the amount of methylmercury entering the hair follicle from the bloodstream and thus reflects the systemic concentration (Myers et al. 2003).[1] Umbilical-cord blood concentration would be expected to correlate most closely with fetal-brain concentration during late gestation (NRC 2000).

Two of the epidemiologic studies used in EPA's risk assessment—those conducted in the Faroe Islands and New Zealand (Kjellström et al. 1986; Kjellstrom et al. 1989; Grandjean et al. 1997)—documented a significant inverse biomarker-neurodevelopment relationship.[2] Effects included poor performance on a number of tests—tests of attention, fine-motor function, language, visual-spatial abilities, and verbal memory. The magnitude of the deficits was consistent with increases in the number of children struggling to keep up in school or requiring remedial action (Rice et al. 2003). Those effects correlated with hair mercury in both studies; cord blood showed the

[1]Human pharmacokinetic studies indicate that methylmercury has a half-life in blood and the whole body of about 50 days (CDC 2005). Hair grows at about 1 cm/month with a delay of around 20 days between current blood concentration and appearance of mercury in hair (Myers et al. 2003). Thus, postnatal maternal hair can be analyzed sequentially to evaluate timing of methylmercury exposure during pregnancy. However, the potential that this affords to document critical periods of prenatal methylmercury exposure has yet to be realized.

[2]On the basis of maternal hair concentration, the third study (conducted in the Seychelles) did not find any association between prenatal methylmercury exposure and adverse neuropsychologic effects (Myers et al. 2003). Reasons for the discrepancies are not known but have been suggested to include differences in the child's age at testing, genetic susceptibilities of the populations, patterns of exposure (episodic vs continuous), and coexposure to polychlorinated biphenyls in the Faroes but not Seychelles populations (Rice et al. 2003).

strongest association with the effects in the study where it was analyzed (Grandjean et al. 1997). The National Research Council (2000) analysis of the epidemiologic studies selected the Faroe Islands study as the lead dataset for dose-response modeling (NRC 2000). After that, EPA conducted a benchmark dose analysis of the cord blood-neurotoxicity relationship stemming from the Faroe Islands dataset (Rice et al. 2003); it yielded a biomarker benchmark dose of 58 μg/L (a cord-blood concentration of 58 μg/L is the 95% lower confidence limit of the dose associated with a 5% increase in neurodevelopmental effects). EPA used a one-compartment model to extrapolate from cord-blood mercury to the corresponding methylmercury intake by the mother. An uncertainty factor of 10 was incorporated into the risk assessment to account for intraindividual variability. The resulting reference-dose (RfD) calculations yielded 0.1 mg/kg per day (Rice et al. 2003).

Recent biomonitoring data from the 1999-2000 National Health and Nutrition Examination Surveys (NHANES) have been used to estimate the proportion of newborn infants in the United States that have been exposed to mercury in utero at above the EPA RfD (Mahaffey et al. 2004). The consumption of methylmercury from fish and other seafood constitutes the main source of dietary mercury exposure in the general population (CDC 2005). Analyses indicate that U.S. women of reproductive age generally have blood mercury below 58 μg/L. However, an estimated 5.7% have blood mercury between 5.8 μg/L and 58 μg/L (CDC 2005; Mahaffey et al. 2004). It has been estimated that in the United States more than 300,000 newborns each year are exposed to methylmercury in utero at concentrations above the RfD (Mahaffey et al., 2004) and within 10-fold of the concentrations associated with a 5% increase above background in neurodeveopmental effects. There has been controversy regarding the extent to which exposures above the RfD, but below 58 μg/L, translate into risk. However, an analysis estimated that 8,000 children are born each year in the United States with cord mercury levels 3.8 times the RfD or at exposure levels similar to those among women in the Faroe Islands (Clewell and Crump 2005). Exposures at this level were estimated to correspond to changes in the mean test score of 1.6% for neuropsychological function that were used in the Faroe Island research (the Boston naming test) (Clewell and Crump 2005). In addition, blood mercury in excess of 58 μg/L has been documented among some groups that consume much fish, including anglers, subsistence fisherman, and members of some American Indian tribes (Mahaffey et al. 2004).

This illustration shows how biomarker-based risk posed by methylmercury (5.8 μg/L as a blood equivalent of the RfD and 58 μg/L as a minimal effect concentration in human fish-eating populations, according to benchmark dose analysis) can be used directly to interpret population biomonitoring data. Pathway analyses conducted by others (Stern et al. 2001; Carrington

and Bolger 2002) have shown that some species of fish may be the most important source of methyl-mercury exposure; this presents a potential for intervention and future lowering of biomonitored concentrations.

Case Examples of Use of Pre-existing Risk Assessments to Interpret Biomonitoring Data: Glyphosate and Permethrin

As described in Chapter 5, one source of information that may assist in the interpretation of biomonitoring data is a pre-existing risk assessment. An example is glyphosate, a commonly used herbicide for which a traditional risk assessment is available from EPA as part of its reregistration evaluation (62 Fed. Reg. 17723 [1997]). The risk assessment estimates general population dietary exposures to be 0.001-0.01 of the acute and chronic RfDs, even if infants and occupationally exposed groups are considered. General-population biomonitoring data on glyphosate are not available, but the urinary biomarker data available on farmers and their families (Acquavella et al. 2004) can be interpreted in light of EPA risk projections.

Another example is permethrin, an insecticide widely used on food crops and in residential and occupational settings (ATSDR 2003). A comprehensive exposure and risk assessment for permethrin by EPA analyzed a number of scenarios for the general population and for homeowner and professional spray appliers (70 Fed. Reg. 51790 [2005]). The analysis of general population exposure via food and drinking water did not find a substantial health risk. However, the residential and worker pesticide spray scenarios were associated with greater risks. Biomonitoring results for the permethrin metabolites urinary *cis*- and *trans*-3-3(2,2,-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid show a highly skewed distribution with the majority of the population having no detectable metabolites and the upper 95th percentile having biomarker concentrations that are many times above the limit of detection (CDC 2005). The NHANES study design was intended to be representative of the general population, so one can tentatively evaluate the median biomarker results for permethrin in light of EPA's general population risk assessment. Furthermore, the upper tail of the distribution may be considered in light of EPA's pesticide application scenarios. An improved biomonitoring study design in which information is gathered on personal pesticide use would help to clarify the exposure assignments. The EPA assessment also shows that the highest potential risks are for toddlers from carpet contact after pesticide application. That shows that a potentially important subgroup was not part of the NHANES biomonitoring dataset in that children under 6 years old were not monitored.

There are numerous caveats in the use of pre-existing risk assessments to interpret biomonitoring datasets, especially if it is not possible to relate the biomonitoring result to the exposure dose and if the population that the

risk assessment was based on differs in some way from the biomonitored population. Other caveats apply case by case. For the permethrin example, the biomonitoring data present issues of biomarker nonspecificity (cypermethrin and cyfluthrin also generate the urinary biomarkers, and a mix of permethrin biomarkers may be most informative), and there are detection-limit issues, as evidenced by the preponderance of nondetection results. The permethrin risk assessment also carries the uncertainty that the potential for developmental toxicity after chronic exposures has not been adequately tested (Shafer et al. 2005).

Case Example of Use of One-Compartment Pharmacokinetic Model to Estimate Intake Dose of Slowly Cleared Lipid-Soluble Chemicals: 2,3,7,8-TCDD

Chapter 5 describes a simple one-compartment modeling approach that can yield screening-level estimates of intake dose based on biomonitoring results (chemical concentration in blood or lipid) for slowly cleared lipid-soluble chemicals. The overall approach is shown below (Figure B-1 is reproduced from Chapter 5):

A basic lipid-partitioning approach similar to that outlined above has been used for TCDD (van der Molen et al. 1996; Lorber and Phillips 2002; EPA 2003), organochlorine pesticides (LaKind et al. 2000; Lindstrom et al. 1976a), and polychlorinated biphenyls (PCBs) (Lutz et al. 1984). For application to interpreting biomonitoring results, the first step is conversion of the blood concentration to total body burden of chemical. For highly lipid-soluble chemicals that do not appreciably bind to proteins, that involves scaling up from the blood concentration with calculations that first express the concentration in blood on a lipid basis (TCDD concentration in blood lipid). The next step is to convert the lipid concentration to a total body burden by multiplying the blood concentration (lipid basis) by the total amount of lipid in the body. That assumes that the chemical will have the

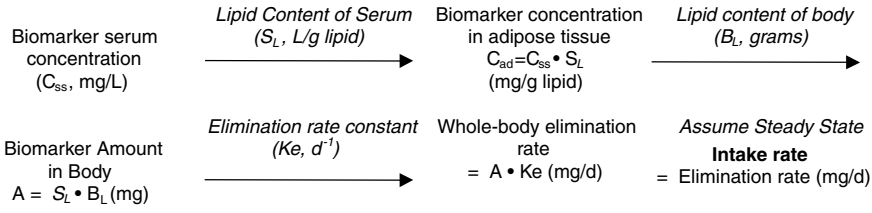

FIGURE B-1 Conversion of biomonitoring data to daily dose on the basis of one-compartment (body-burden) model.

same concentration in all lipid compartments of the body. The resulting body burden undergoes a daily loss at a rate based on its elimination via renal or, in the case of TCDD, hepatic (metabolic) clearance. The long-term rate of elimination from blood is used because it represents true clearance from the body without the influence of continuing absorption or chemical redistribution. Although such half-life information has been estimated in humans for organochlorines, it is not quite accurate, because there is typically low-level exposure after earlier periods of higher (for example, occupational) exposure. Nevertheless, such total-body clearance rates can provide a useful estimate for calculating the daily clearance rate, which, under the assumption of steady state (no change in body burden), must be balanced by chemical intake.

The one-compartment approach has been used to estimate background exposure to TCDD in the general population on the basis of serum or adipose measurements with the following equation (EPA 2003):

$$\text{Dose} = [(0.693/t_{1/2})(\text{volume body fat})(\text{concentration in body fat})(CF_1 * CF_2)] / \text{fraction absorbed},$$

where dose is in picograms per day, half-life ($t_{1/2}$) is in years, volume body fat is in kilograms, concentration in body fat is in picograms per kilogram, CF_1 is a conversion factor in grams per kilogram, and CF_2 is a conversion factor in years per day.

For TCDD and related congeners, a traditional pathway analysis has also been conducted. The daily dose estimated from extrapolation of biomonitoring results is in a similar range as the estimates from exposure-pathway calculations (EPA 2003). That suggests that the conversion of biomonitoring results to an exposure dose may be feasible when pharmacokinetic information (chemical half-life in humans) is relatively sparse. However, this applies only to steady-state conditions in which the biomonitoring result reflects a stable level from long-term storage in lipid with slow elimination. Under those conditions, it is fairly straightforward to calculate body burden and thus convert the long-term half-life to a total-body loss rate that one assumes (at steady state) is matched by the intake rate. That approach may be applicable to PCBs and other persistent organochlorines, but it is less feasible for other types of chemicals.

A caveat with this approach is the potential for variability in elimination rate. The biologic half-life of TCDD has been estimated at 3-27 years in people chronically exposed to TCDD; central-tendency half-lives are reported as 5.8-8.7 years in various studies (Pirkle et al. 1989; Michalek et al. 1996; Ott and Zober 1996). At least some of the variability is due to different sizes of the body lipid compartment and to variable activity of the CYP1A family to metabolize TCDD (EPA 2003). In fact, there is some

support for the idea that the higher the TCDD body burden, the shorter the half-life, because TCDD induces the CYP1A family of enzymes through which it is metabolized (Carrier et al. 1995). There is also greater binding to hepatic proteins when metabolizing systems are induced by TCDD, and this alters chemical distribution (Abraham et al. 1988). A recent PBPK modeling approach for dioxin takes into account inducible elimination (Emond et al. 2005a); PBPK modeling of PCBs was recently used to simulate changing blood concentrations over short periods (Emond et al. 2005b).

Case Examples of Interpretation of Biomonitoring Results for Rapidly Cleared Chemicals Under Non-Steady-State Conditions: Chlorpyrifos and Trichloroethylene

Chlorpyrifos

Chlorpyrifos provides an example of the utility of human pharmacokinetic models to estimate daily dose from biomonitoring data for a rapidly cleared pesticide. The urinary metabolite trichloro-2-pyridinol (TCP) is used in the NHANES study to monitor population exposure to chlorpyrifos (CDC 2005). Several epidemiologic studies have linked chlorpyrifos exposure to adverse birth outcomes through associations between urinary and blood biomarkers and have demonstrated maternal exposure and physiologic measurements in the neonate (Berkowitz et al. 2003, 2004; Whyatt et al. 2004; Needham 2005).

However, chlorpyrifos exposures among the populations evaluated in these studies may have been higher than in the general population. Recent NHANES data suggest that regulatory limits on chlorpyrifos use in residential settings have succeeded in decreasing general population exposures compared with 1988-1994 (Barr et al. 2005; CDC 2005).

Further interpretation of urinary biomonitoring data has been attempted with pharmacokinetic simulations by using a relatively simple one-compartment model to convert urinary concentrations to intake doses (Rigas et al. 2001; Shurdut et al. 1998; Barr 2005). The key assumption needed for back-calculation of intake dose from urinary concentration is that 70% of the dose is excreted in the urine as TCP over a relatively short period.

Pharmacokinetic calculations yielded estimates of chlorpyrifos intake of 0.05-1 μg/kg per day in the general population. The model estimates compare favorably with pathway analysis estimates of aggregate chlorpyrifos exposure from numerous dose routes, including indoor inhalation, dermal contact, and food ingestion (Shurdut et al. 1998; Pang et al. 2002). The calculated exposure doses ranged from 0.02 to 1 μg/kg per day. Further

refinements in both the pharmacokinetic modeling and exposure pathway analyses may help to narrow the range of estimated doses.

A more detailed seven-compartment human PBPK model for chlorpyrifos was calibrated against pharmacokinetic data in human subjects (Timchalk et al. 2002). The model can predict urinary output of TCP for a wide range of chlorpyrifos doses and exposure scenarios and so may be useful in refining the interpretation of population biomonitoring. That may be particularly important because the degree to which population biomonitoring results reflect steady-state conditions is not known and, for a rapidly eliminated biomarker, requires fairly constant exposure. More advanced modeling approaches can derive the biomonitoring serum concentration with a variety of different exposure scenarios (such as isolated bolus exposures vs low-level continuous exposures) in a sensitivity analysis to explore the risk implications of particular biomonitoring results (Rigas et al. 2001).

An important caveat in interpreting chlorpyrifos metabolite concentrations in urine is that this metabolite (TCP) is widespread in the environment and thus can appear in urine as a result of direct intake as well as from conversion from a parent chemical (Lu et al. 2005; Wilson et al. 2003). For example, the concentration of TCP in foods can be greater than that of chlorypyrifos, and concentrations in house dust can be generally comparable (Morgan et al. 2005). Direct intake of TCP from environmental media makes extrapolation of urinary biomarker concentration to chlorpyrifos exposure dose uncertain.

Trichloroethylene

Solvents are typically not targeted for biomonitoring in general population studies, because their rapid clearance by exhalation or metabolism results in a transient biomarker that does not reach steady state. However, analysis of such rapidly cleared chemicals may be possible, as exemplified in a trichloroethylene (TCE) biomarker study (Sohn et al. 2004), which constitutes another case study of pharmacokinetic modeling of human biomonitoring data under non-steady-state conditions.

The biomonitoring data are based on a study of eight subjects exposed in a chamber for 4 hours to TCE at 100 ppm (Fisher et al. 1998). TCE blood concentrations were followed during exposure and for 12 hours afterward to demonstrate the buildup of TCE and its clearance from blood in each subject. (TCE is eliminated from blood rapidly, with a half-life of minutes to hours.)

A PBPK model was used to simulate the data but was then analyzed in reverse, starting with blood concentrations but missing the exposure infor-

mation (TCE concentration, sampling time, and exposure duration). The goal was to determine whether a Bayesian inference approach could be used to predict the exposure conditions for the eight subjects on the basis of their biomarker data and the PBPK model. Initial predictions of TCE blood concentrations were based on a set of "priors," or modeling starting points. Monte Carlo analysis was used to present a full spectrum of TCE blood concentrations by using distributions rather than point estimates for a variety of PBPK modeling inputs. Because the "prior" information did not include exposure information, the initial TCE blood estimates were highly variable and not very precise. The updated, or "posterior," estimates were based on a backfit that minimized the error between the model-predicted and actual biomonitoring data. The reconstructed exposure profiles yielded estimates of TCE concentration in air and other exposure characteristics (onset and duration) that were reasonably close to the actual experiment, although there was still a large degree of uncertainty in the estimates. The uncertainty could probably be reduced by improved information on behaviors that lead to exposure; for example, if onset and duration were more certain, TCE air concentration estimates would be improved.

Fisher 1998 demonstrates that the more that is learned about the biomarker (half-life, time course in blood or urine, and development of PBPK model) and the exposed population (age, body weight, pharmacogenetic traits, behavioral factors that affect exposure, and time between exposure and sample measurement), the more refined dose estimates can become. Without such information, a highly transient metabolite like TCE is not a reliable marker of exposure, unless exposure is nearly continuous and uniform. That may not be the case in the general population, so TCE in blood may not be a good biomarker for assessment of general-population exposure, although PBPK models are available to extrapolate from biomarker concentration to external dose in both animals and humans (Clewell et al. 2000).

PBPK and Bayesian inference approaches analyze multiple sources of uncertainty and variability and thus have the potential to improve estimates of exposure (for example, time-weighted average air concentration) from TCE concentrations in blood. However, those techniques are data-intensive and time-consuming (although no more demanding than other methods of back-estimation). A simpler bounding approach may be useful as a first step in trying to reconstruct an exposure dose from biomonitoring data on short-lived biomarkers. Figure B-2 shows a simulated blood-concentration curve for a volatile organic chemical like TCE after a bolus exposure. A particular biomonitoring blood concentration can come from any point along the time course because it is not known when the sample was taken relative to the exposure events (sampling-time variability). If one assumes that the sample came from the left end of the curve (Figure B-2), reflecting

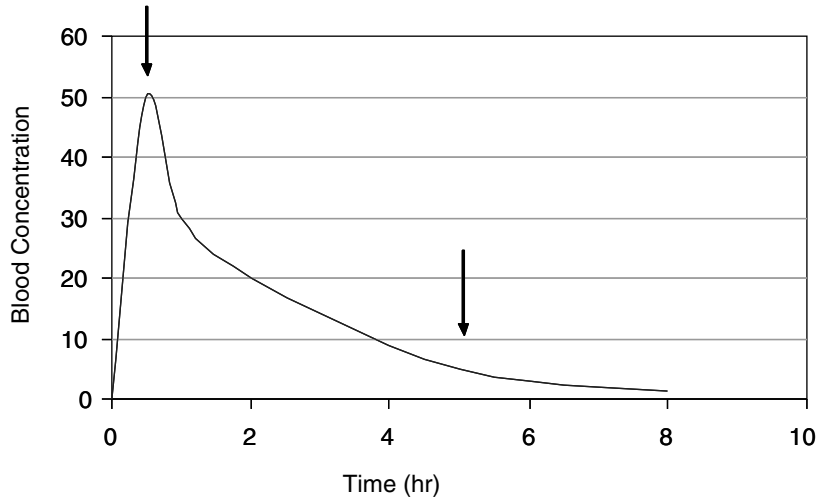

FIGURE B-2 Time course for VOC concentrations in blood after a bolus dose. Arrows indicate two of the many time points when a biomonitoring sample may be taken. Without prior knowledge, a useful screening approach is to assume that the sample was taken at the 5-hour arrow, well after the peak blood concentration. If that assumption is used across the population, a pharmacokinetic model can yield reasonably conservative bounding estimates of exposure dose. (Many exposure events might occur in a single day that could affect the concentration-time course of the VOCs in blood.)

peak internal exposure (first arrow), the PBPK model will predict a relatively low exposure concentration. If one assumes that the sample came from a late time when most TCE is washed out of the blood (second arrow), the model will convert this biomonitored concentration to a high exposure dose.

Thus, for screening purposes, one can project high-end exposure doses for rapidly cleared biomarkers by running the human PBPK model with the assumption that the sample was taken after multiple half-lives had elapsed from the exposure event. The high-end exposure estimates could be used in an initial risk assessment to compare with the RfD or other toxicity benchmarks. If the risk estimate is below a level of concern, there may not be a need for a more refined analysis. However, if it is high, it will trigger a more complete analysis in which the entire pharmacokinetic profile will be used in a probabilistic (Monte Carlo) setting that involves inference techniques. A high degree of variability in the biomonitoring data or many overlapping exposure episodes in a single person would make these approaches more complex but still valuable. The more information on the exposure and

sampling events (for example, samples collected in a clinic away from the home environment and thus several hours away from exposure sources), the more refined the dose prediction.

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Appendix C

PBPK Modeling

By R.S.H. Yang[1]

WHAT IS PHYSIOLOGICALLY BASED PHARMACOKINETICS? WHAT ARE THE DIFFERENCES BETWEEN PBPK AND CLASSICAL PHARMACOKINETICS?

Physiologically based pharmacokinetics (PBPK), as the name implies, is a special branch of pharmacokinetics where physiology and anatomy of the animal or human body, as well as the biochemistry of the chemical or chemicals of interest, are incorporated into the conceptual model for computer simulation. "Classical pharmacokinetics" refers to those empirical noncompartmental or compartmental pharmacokinetic studies routinely practiced in pharmaceutical industry (van de Waterbeemd and Gifford 2003). As will be illustrated later, the compartments of a PBPK model have anatomical and physiological significance. This is a major difference from empirical noncompartmental or compartmental pharmacokinetic modeling approaches. PBPK models can be used to describe concentration-time profiles in individual tissue/organ and in the plasma or blood. When the concentration of a certain target tissue, rather than the plasma concentration, is highly related to a compound's efficacy or toxicity, PBPK modeling will be a more useful tool than classical pharmacokinetic models for describing PK/

[1]Excerpted primarily from Yang, R.S.H., M.E. Andersen, J.E. Dennison, Y.C. Ou, K.H. Liao, and B. Reisfeld, 2004. Physiologically based pharmacokinetic and pharmacodynamic modeling. Pp. 391-405 in *Mouse Models of Cancer*. E.C. Holland, ed., Wiley: New York. Reprinted with permission; copyright 2004, Wiley.

PD relationship and thus make a better prediction of the time course of drug effects resulting from a certain dose regimen for the compound of interests. Furthermore, PBPK models in combination with absorption simulation and quantitative structure-activity relationship (QSAR) approaches will bring us closer to a full prediction of drug disposition for pharmaceutical new entities, and help streamline the selection of lead drug candidate in the drug discovery process (van de Waterbeemd and Gifford 2003). Lastly, unlike empirical noncompartmental and compartmental pharmacokinetics, PBPK modeling is a powerful tool for extrapolation, be it for interspecies, inter-routes, inter-doses, inter-life stages, etc.

The concepts of PBPK had its embryonic development in the 1920s and 1940s; for a more detailed early history, the readers are referred to a review (Yang et al. 2004) and a recently published book (Reddy et al. 2005). PBPK modeling blossomed and flourished in the late 1960s and early 1970s in the chemotherapeutic area mainly due to the efforts of investigators with expertise in chemical engineering process design and control. Two notable pioneers in this development are Dr. Kenneth B. Bischoff, then at University of Texas, Austin, TX, and Dr. Robert Dedrick of Biomedical Engineering and Instrumentation Branch, Division of Research Services, National Institute of Health, Bethesda, MD. Two timeless publications by these investigators are, respectively, "*Drug Distribution in Mammals*" (Bischoff and Brown, 1966) and "*Animal Scale-Up*" (Dedrick, 1973); these papers are highly recommended to those who are interested in PBPK modeling. In the mid 1980s, two papers on PBPK modeling of styrene and methylene chloride (Ramsey and Andersen 1984; Andersen et al. 1987) started yet another "revolution" in the toxicology and risk assessment arena. Today, there are more than 700 publications directly related to PBPK modeling on industrial chemicals, drugs, environmental pollutants, and simple and complex chemical mixtures (Reddy et al. 2005).

A PBPK model, graphically illustrated in Figure C-1, reflects the incorporation of basic physiology and anatomy. The compartments actually correspond to anatomic entities such as liver, lung, . . .etc., and the blood circulation conforms to the basic mammalian physiology. In this specific model, an actual published example on methylene chloride, it is quite obvious that the exposure route of interest is inhalation because the lung and gas exchange compartments are prominently displayed with intake (CI) and exhalation (CX) vapor concentrations indicated. Oral and/or dermal exposures may be added easily to the GI tract compartment or general venous circulation, respectively. Some tissues (e.g., richly (poorly) or slowly (rapidly) perfused tissues in Figure C-1) are "lumped" together because there is insufficient evidence to conclude that the component tissues in each of these compartment are kinetically distinct enough, for the specific chemical, to warrant individual separate compartments.

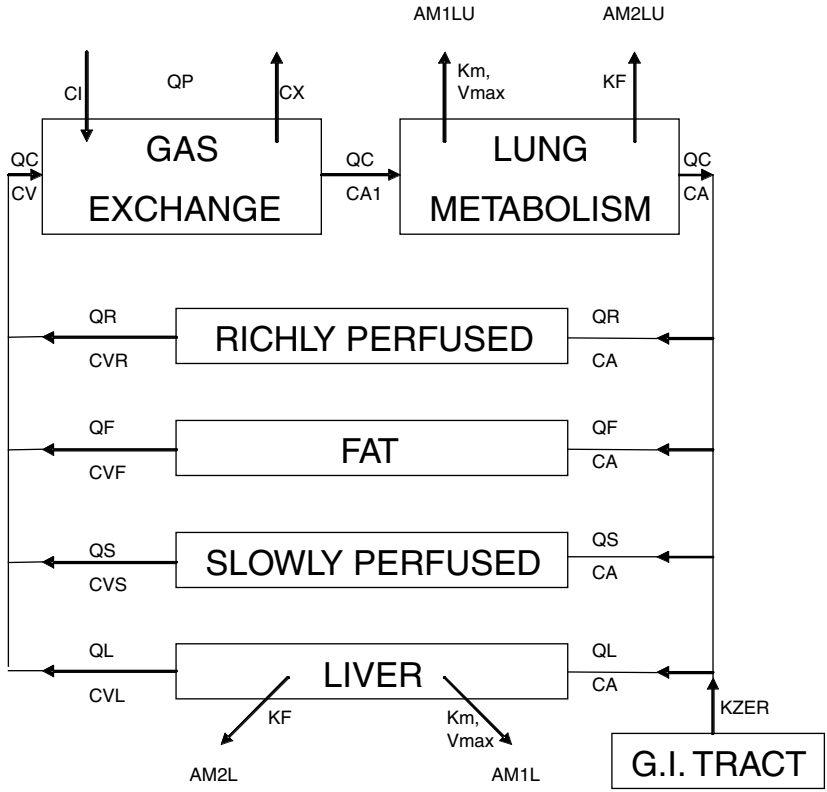

FIGURE C-1 A graphical representation of a physiologically based pharmacokinetic (PBPK) model for methylene chloride. Q represents blood flow; thus, QC, QP, QR, QF, QS, QL are cardiac output, pulmonary blood flow, and blood flows for richly perfused, fat, slowly perfused, and liver compartments, respectively. C represents concentration of the chemical we are studying; thus, CI, CX, CV, CA, CVR, CVF, CVS, CVL are concentrations in inhaled breath, exhaled breath, venous blood, arterial blood, richly perfused, fat, slowly perfused, and liver compartments, respectively. K_m, V_{max}, K_F are metabolic parameters representing affinity constant, maximum rate constant for Michaelis-Menton enzyme kinetics (saturation or nonlinear kinetics), and first order rate constant (linear kinetics), respectively. AM1LU, AM2LU, AM1L, AM2L are, respectively, amount of metabolite 1 or 2 for lung (LU) and liver (L). Source: Andersen et al. 1987. Reprinted with permission; copyright 1987, *Toxicology and Applied Pharmacology*.

If one draws an analogy of the "scale-up" from a laboratory chemical engineering process to a chemical plant to the "scale-up" of a mouse to a human, one finds that both situations are governed by a great number of

physical and chemical processes. In mammals, the physical processes (i.e., mass balance, thermodynamics, transport, and flow) often vary in a predictable way. However, chemical processes such as metabolic reactions may vary greatly and less predictable among species. These physical and chemical processes interact in the body such that the pharmacokinetics of any given chemical between one species and another may be more (or less) predictable depending on the amount of background information available.

HOW DOES A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL WORK?

A PBPK model applies fundamental physiological, biochemical, and engineering principles to describe the distribution and disposition of chemicals in the body at any given time. The process and approach may be summarized in a flow chart (Figure C-2). Once the chemical of interest and the problems needing to be addressed are identified, a thorough literature evaluation is conducted. Three sets of parameters are needed for PBPK model building: physiological parameters (e.g., ventilation rates, cardiac output, organs as % body weight), thermodynamic parameters (e.g., tissue partition coefficients, flow rates), and biochemical parameters (e.g., K_m and V_{max}). Most, if not all, of the parameters for laboratory animals are available in relevant literature such as the Biological Data Book, and the special report by the International Life Sciences Institute (ILSI) on the compilation of physiological parameters for PBPK models (Brown et al. 1997). When information gaps exist, the solution is either an empirical one via experimentation or through allometric extrapolation, usually based on a power function of the body weight (Lindstedt 1987).

The fundamentals of PBPK modeling are to identify the principal organs or tissues involved in the disposition of the chemical of interest and to correlate the chemical absorption, distribution, metabolism, and excretion within and among these organs and tissues in an integrated and biologically plausible manner. A scheme is usually formed where the normal physiology is followed in a graphical manner (i.e., a conceptual model as in Figure C-1). Within the boundary of the identified compartment (e.g., an organ or tissue or a group of organs or tissues), whatever 'comes' in must be accounted for via whatever 'goes out' or whatever is transformed into something else. This "mass balance" is expressed as a mathematical equation with appropriate parameters carrying biological significance. For instance, "a general equation, for any tissue or organ, is:

$$Vi\frac{dC_{ij}}{dt} = Q_i(CA_j - CV_{ij}) - \mathrm{Metab}_{ij} - \mathrm{Elim}_{ij} + \mathrm{Absorp}_{ij} - \mathrm{PrBinding}_{ij},$$

where V_i represents the volume of tissue group *i*, Q_i is the blood flow rate to tissue group *i*, CA_j is the concentration of chemical *j* in arterial blood, and C_{ij} and CV_{ij} are the concentrations of chemical *j* in tissue group *i* and in the effluent venous blood from tissue *i*, respectively. $Metab_{ij}$ is the rate of metabolism for chemical *j* in tissue group *i*; liver, being the principal organ for metabolism would have significant metabolism and, with some exception, usually $Metab_{ij}$ is equal to zero in other tissue groups. $Elim_{ij}$ represents the rate of elimination from tissue group *i* (e.g., biliary excretion from the liver), $Absorp_{ij}$ represents uptake of the chemical from dosing (e.g., oral dosing), and $PrBinding_{ij}$ represents protein binding of the chemical in the tissue." All these terms are zero unless there is definitive knowledge that the particular organ and tissue of interest has such processes (Yang et al. 2005).

A series of such mass balance differential equations representing all of the interlinked compartments are formulated to express a mathematical representation, or model, of the biological system. This model can then be used for computer simulation to predict the time course behavior of any given parameter in the model.

For the most well-studied chemicals or drugs, it is likely that the biochemical constants such as K_m's and V_{max}'s are known and readily retrievable from the information data base. However, it must be made clear here that the K_m, V_{max}, and K_F (first order rate constant) in a PBPK model (known as in vivo K_m, V_{max}, K_F for a given chemical) such as the ones given in Figure C-1 are hybrid constants of all the saturable or linear metabolic pathways, respectively, for the chemical of interest in the organ and/or body. They are different from the in vitro K_m, V_{max}, or K_F of a given pure enzyme. While they are not directly interchangeable, the in vitro constants in the literature may be used to estimate in vivo constants for modeling purposes (Lipscomb et al. 1998; Kedderis and Lipscomb 2001). Also, for most well-known chemicals, it is likely that enough is known about the mechanism of toxicity to be incorporated into the model for computer simulation. The physiological constants such as organ volumes, blood flow rates, etc., are usually available in the literature for the common laboratory animals as well as humans. Therefore, at least in those instances of "well-known" chemicals, a model may be conceptually illustrated as in Figure C-1, and mathematically represented by a number of mass balance differential equations. Computer simulations may be made for any number of desired time-course endpoints such as the blood levels of the parent compound, liver level of a reactive metabolite, and similar information on different species, at lower or higher dose levels, and/or via a different route of exposure. The experimental pharmacokinetic data may then be compared with PBPK model simulation to see if it is superimposable upon each other. If this is indeed the case, the model is consistent with actual results. "Validation" of the PBPK model with data sets other than the working set

(or training set) to develop the model is necessary. We put the word "validation" in quotation mark because there are scientists who don't really believe that there is such a thing as "model validation." The most important thing to remember is that model is usually an over-simplification of reality; thus, "all models are wrong, some are useful" as stated by George Box. In such "validation" processes, the more the PBPK model is validated with other data sets, the more robust the model is in its predictive capability. Once "validated," the PBPK model is ready for extrapolation to other animal species including humans. However, if the experimental data and PBPK model simulation are not consistent, the model might be deficient because critical scientific information might be missing or certain assumptions are incorrect. The investigator, with knowledge of the chemical and a general understanding of the physiology and biochemistry of the animal species, can design and conduct critical experiments for refining the model to reach consistency with experimentation (Figure C-2). This refinement

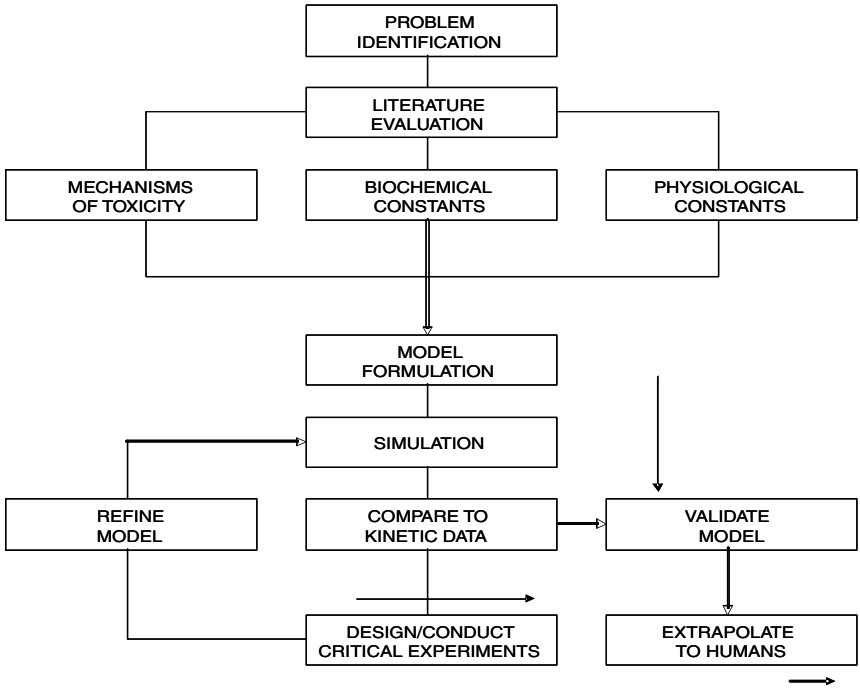

FIGURE C-2 A flow chart illustrating processes involved in physiologically based pharmacokinetics. Source: Andersen 1987. Reprinted with permission; copyright 1987, *Toxicology and Applied Pharmacology*.

process may be repeated again and again when necessary; such an iterative process is critically important for the development of a PBPK model. In that sense, PBPK modeling is a very good hypothesis-testing tool in toxicology and it may be utilized to conduct many different kinds of experiments on computer (i.e., in silico toxicology). It should be noted that there is always the possibility that a good model may not be obtained at the time because of the limitation of our knowledge on the chemical.

Physiologically Based Pharmacodynamic Modeling

Using plain English, pharmacokinetics can be considered as "What the body does to the chemicals," and pharmacodynamics can thus be considered "What the chemicals do to the body." Physiologically based pharmacodynamic (PBPD) modeling is therefore computer simulation of pharmacological or toxicological effects of chemicals or drugs, based on the biology of chemical/drug-receptor interactions. From the point of a chemical or a drug enters into the body to the point of pharmacological or toxicological effect, it is a continuum of pharmacokinetics and pharmacodynamics. It is difficult to distinguish where pharmacokinetics end and pharmacodynamics start. Having said that, however, this Appendix is centered around PBPK modeling; PBPD modeling is outside of the scope of this appendix.

Data Requirements for PBPK Modeling

What are the specific data needed for building PBPK models? Obviously, well conducted in vivo pharmacokinetic data are essential and usually the more the data sets (e.g., different doses, routes, species), the better. In each study, time-course blood and tissue concentration data are essential. These time-course data should include at least the following tissues and organs: blood (or plasma if blood cell binding is not an issue), liver (organ of metabolism), kidney (representing well-perfused organs/tissues), muscle (representing slowly-perfused organs/tissues), and target organ(s)/tissue(s). We also need other PBPK-modeling specific information such as: (1) physiological constants, including body size, organ and tissue volumes, blood flow and ventilation rates; (2) biochemical constants, including the chemical-specific metabolic rate constants such as V_{max} and K_m, partition coefficients for tissues; and (3) mechanistic factors such as target tissues, metabolic pathways, and receptor interactions. Enzyme kinetic data, particularly human data, of at least the key metabolic processes will be important for the PBPK model. In vitro determination of tissue partition coefficients and enzyme kinetic data are relatively straightforward and inexpensive. With modern genetic engineering technologies, many human enzymes are available commercially. Thus, heretofore unavailable human

enzyme kinetic information for many of the environmentally important chemicals are within easy reach for many laboratories.

PBPK Models for Chemical Interactions (Interactive PBPK Models)

Human exposure to chemicals is rarely, if ever, to single chemicals. The most ideal and scientifically defensible data requirement for establishing an interactive PBPK model is that each component chemical in the mixture already has its respectively established PBPK model and that there are many pharmacokinetic data sets in laboratory animals as well as in humans available for each of these component chemicals. The interactive PBPK model is then built on the basis of known pharmacokinetic interactions. For instance, the component chemicals may inhibit each others' biotransformation. The individual PBPK models may then be linked together at the liver compartment by introducing competitive inhibition (or other types of inhibition) terms in the mass balance differential equation. Even though PBPK modeling of chemical mixtures is necessary in the cumulative risk assessment, this area is very complex and it is still an emerging field. For a more thorough discussion, the readers are referred to additional references on PBPK modeling of chemical mixtures (Krishnan et al. 2002; Yang and Andersen 2005).

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Glossary

ACC: American Chemistry Council.

Accuracy: Reflects the agreement between the measured value and the "true" value.

ACGIH: American Conference of Governmental Industrial Hygienists.

AHS: Agricultural Health Study.

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome.

ATSDR: Agency for Toxic Substances and Disease Registry.

AUC: Area under the concentration-time curve.

BAT: Biologic Tolerance Value for Occupational Exposures.

BED: Biologic effective dose is the amount of a chemical or its metabolite that interacts with critical subcellular, cellular, and tissue targets.

BEIs: Biological exposure indices are the concentrations of chemicals that are most likely to be observed in specimens (blood or urine) collected from healthy workers who have been exposed to chemicals to the same extent as workers with inhalation exposure at the TLV.

Bias: Systematic error.

Biobank or biorepository: A system that will store one or many types of biologic specimens for later analysis from single or multiple studies under conditions that permit efficient retrieval and optimum stability of the sample.

Biologic effects: These may include a wide range of observations, from very early biochemical perturbations to clinical signs of alteration of health.

Biomarker of effect: A measurable biochemical, physiologic, behavioral, or other alteration in an organism that, depending on the magnitude, can be recognized as associated with an established or possible health impairment or disease.

Biomarker of exposure: The chemical or its metabolite or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism.

Biomarker of susceptibility: An indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific chemical substance.

Biomonitoring: Defined as one method for assessing human exposure to chemicals by measuring the chemicals or their metabolites in human specimens, such as blood or urine.

Cancer slope factor: An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent.

CDC: Centers for Disease Control and Prevention.

CERHR: Center for the Evaluation of Risks to Human Reproduction.

Chemical: A chemical compound or element present in air, water, food, soil, dust, or other environmental medium (such as consumer products).

CLIA: Clinical Laboratory Improvement Act.

CLSI: Clinical and Laboratory Standards Institute.

Creatinine: An end-product of protein metabolism found in the blood and urine.

DEHP: diethylhexylphthalate.

EBE: Early biological effect represents an event correlated with, and possibly predictive of, a health effect.

EPA: Environmental Protection Agency.

EPIC: European Prospective Investigation into Cancer and Nutrition.

EWG: Environmental Working Group.

Exposure assessment: An identification and evaluation of the human population exposed to a toxic agent, describing its composition and size, as well as the type, magnitude, frequency, route and duration of exposure.

External dose: Amount of chemical that is inhaled, ingested, or comes in dermal contact and is available for systemic absorption. External dose is usually expressed in units of mg of chemical per kg body weight per day (mg/kg/day).

FDA: Food and Drug Administration.

FFES: Farm Family Exposure Study.

GAO: Government Accountability Office.

GerES: German Environmental Surveys.

Half-life: Time required for an organ, tissue, or the whole body to eliminate (excrete) one-half of the concentration of a chemical or its metabolite.
HIPAA: Health Insurance Portability and Accountability Act.
ID: Internal dose is the amount of a chemical or its metabolite found in a biologic medium.
Intra-individual variability: Biological variation within people.
Interindividual variability: Biological variation between people.
ILSI: International Life Sciences Institute.
IOM: Institute of Medicine.
IRB: Institutional review board.
ISBER: International Society for Biological and Environmental Repositories.
LOD: Limit of detection is the lowest concentration that can be measured.
LOAEL: Lowest observed-adverse-effect level.
Metabolite: A chemical alteration, produced by body tissues, of the original compound.
mg/kg/day: Milligrams per kilogram per day.
μg/kg/day: Micrograms per kilogram per day.
MOE: Margin-of-exposure.
NCI: National Cancer Institute.
NCS: National Children's Study.
NHANES: National Health and Nutrition Examination Survey.
NHATS: National Human Adipose Tissue Survey.
NHEXAS: National Human Exposure Assessment Survey.
NHMP: National Human Monitoring Program.
NIEHS: National Institute of Environmental Health Sciences.
NIH: National Institutes of Health.
NIOSH: National Institute for Occupational Safety and Health.
NOAEL: No-observed-adverse-effect level.
NRC: National Research Council.
NTP: National Toxicology Program.
OECD: Organisation for Economic Co-operation and Development.
OSHA: Occupational Safety and Health Administration.
PAHs: Polycyclic aromatic hydrocarbons.
PCBs: Polychlorinated biphenyls.
PBDE: Polybrominated diphenyl ethers.
PBPK: Physiologically based pharmacokinetic model.
PFOA: Perfluorooctanoic acid.
Pharmacodynamics: Biological effect of chemical interaction with target sites in the body.
Pharmacokinetic: The quantitative study of factors that control the time course for absorption, distribution, metabolism, and excretion of chemicals within the body.

Polymorphism A genetic variant that appears in at least 1% of a population.
ppb: Parts per billion.
ppm: Parts per million.
Precision: A measure of the degree of agreement among individual results obtained from the same or identical specimens with the same method and by the same analyst and laboratory.
QA-QC: Quality assurance-quality control.
Reference ranges: Biologic measurements obtained in a reference population, typically a population with no known exposure or only minimal exposure to the toxicant of concern.
RfCs: Reference concentration is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
RfD: Reference dose is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
Risk assessment: The evaluation of scientific information on the hazardous properties of environmental agents (hazard characterization), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment).
RMBC: Rocky Mountain Biomonitoring Consortium.
Robustness: A measure of intralaboratory day-to-day variation induced by small changes in procedure.
Ruggedness: A method's reproducibility under the influence of variation in analyst, instrumentation, day of testing, and laboratory.
SCALE: Science, Children, Awareness-Raising, Legal Instruments and Evaluation is part of a larger European Environment and Health strategy to reduce and prevent diseases related to environmental exposures, with emphasis on exposures of susceptible populations, including children.
SES: socioeconomic status.
SOPs: Standard operating procedures.
Specificity: The ability to identify and quantify the target analyte in the presence of chemically similar interfering compounds.
TCDD: Dioxin.
TCE: Trichloroethylene.
TCP: 3,5,6-trichloro-2-pyridinol.

TLV-TWA: Threshold Limit Value-time weighted average is time-weighted average concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect.

Toxicokinetics: A more recent term that has essentially the same meaning as pharmacokinetics, but refers specifically to non-drug substances, primarily toxic chemicals.

ULV: Upper-limit value.

USDA: United States Department of Agriculture.

VOCs: Volatile organic compounds.

Vd: Volume of distribution.

WHO: World Health Organization.

WWF: World Wildlife Fund