



## Overview

# Human Tissue Monitoring and Specimen Banking: Opportunities for Exposure Assessment, Risk Assessment, and Epidemiologic Research

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A symposium on Human Tissue Monitoring and Specimen Banking: Opportunities for Exposure Assessment, Risk Assessment, and Epidemiologic Research was held from 30 March to 1 April 1993 in Research Triangle Park, North Carolina. There were 117 registered participants from 18 states and 5 foreign countries. The first 2 days featured 21 invited speakers from the U.S. Environmental Protection Agency, the Centers for Disease Control and Prevention, the National Institute of Environmental Health Sciences, various other government agencies, and universities in the United States, Canada, Germany, and Norway. The speakers provided a state-of-the-art overview of human exposure assessment techniques (especially applications of biological markers) and their relevance to human tissue specimen banking. Issues relevant to large-scale specimen banking were discussed, including program design, sample design, data collection, tissue collection, and ethical ramifications. The final group of presentations concerned practical experiences of major specimen banking and human tissue monitoring programs in the United States and Europe. The symposium addressed the utility and research opportunities afforded by specimen banking programs for future research needs in the areas of human exposure assessment, risk assessment, and environmental epidemiology. The third day of the symposium consisted of a small workshop convened to discuss and develop recommendations to the U.S. Environmental Protection Agency regarding applications and utility of large-scale specimen banking, biological monitoring, and biological markers for risk assessment activities. — *Environ Health Perspect* 103(Suppl 3):3-8 (1995)

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## Background

Over the last 60 years, human technologies and activities have created and released an unprecedented diversity and quantity of toxic substances into the environment. As we have learned more about the actual and potential adverse effects of these pollutants on the global ecosystem, in general, and on human health, in particular, there has been a growing recognition of the need to monitor the release and subsequent movement of these substances through both the physical and biological components of the environment. In addition to the sampling and monitoring of the ambient outdoor environment for toxic pollutants, there has been an increasing interest in both the monitoring of

human tissues for toxic substances (1) and the assessment of total human exposure to toxic substances from all outdoor and indoor sources (2,3). These approaches have been further stimulated by recent scientific and technical advances in the areas of population sampling design and sampling techniques, microenvironmental monitoring, personal exposure monitoring devices, survey instrument design, direct quantification methods for toxic substances or their metabolites in human tissue samples, development and use of biological markers, and quality control and quality assurance methodologies (4).

Biological monitoring involves the periodic measurement of toxic substances or their metabolites in samples of tissues, secretions, excretions, or exhaled air from biological specimens or individuals. To serve a primary monitoring function, sample selection and collection must be designed to be representative of a defined target population or geographic area over a specific time period. Biological monitoring could thus serve an important sentinel function in detecting the occurrence of a

widespread toxic exposure at an early stage, before the toxic exposure becomes evident as a widespread occurrence of adverse health effects.

Human tissue monitoring may also provide more accurate measurement of internal dose for certain chemicals that occur in relatively low concentrations in the environment but become progressively more concentrated along successive links of the food chain to humans. Furthermore, measuring toxic chemicals (or their metabolites) directly in the appropriate tissues of an individual can often indicate the cumulative dose of the toxic chemical over a period of time from all possible environmental pathways and routes of entry into the body (provided the toxic substance remains in the tissue for a sufficiently long period of time). For example, most organochlorine pesticides or their metabolites persist in the environment and in human tissues. Measurable amounts of many organochlorine pesticides or their metabolites were found to be ubiquitous in human tissue samples collected from across the United States during the 1970s (5,6).

This paper is an overview of the Conference on Human Tissue Monitoring and Specimen Banking: Opportunities for Exposure Assessment, Risk Assessment, and Epidemiologic Research held 30 March–1 April 1993 in Research Triangle Park, North Carolina.

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Similarly, during the late 1960s and early 1970s, polychlorinated biphenyls (PCBs) were recognized as persistent environmental contaminants. Bioaccumulation of PCBs in plants and animals resulted in their concentration in the food chain to humans (7) and their detection in human tissues (8,9).

As these advances in exposure assessment were occurring, the field of environmental specimen banking was also progressing. Environmental specimen banking is the 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 (10). Such specimens would be available to measure levels of environmental pollutants (or their metabolites or other markers of their presence) and, in the case of biological specimens, to detect and quantify biological markers of dose or biological response (11).

The archival collection and storage of human tissue samples provides a unique research opportunity for advancing the science and technology of human exposure assessment. Banked tissue specimens collected as part of national surveys could serve as historical records of human exposures to toxic substances in time and space and so could be a critical part of a comprehensive program of biological monitoring for toxic pollutants. Banked specimens would be available for retrospective studies using more sensitive, complete, or comprehensive analytic techniques at a later time with the benefits of both hindsight and more advanced technological capabilities. Within the limitations of the sampling frame originally designed for the collection of particular specimen banks, they could, for example, be used to measure additional toxic substances not originally studied, baseline values for toxic substances not presently recognized as environmental hazards, and past exposures suspected of causing diseases with very long latency periods. Furthermore, specimen banks could also be used to measure standards for assessing status and trends in human exposure and help evaluate the efficacy of actions taken to prevent or reduce exposure. Large specimen banks built from large cohort studies provide the opportunity to design and carry out very cost-effective nested case-control studies (12,13).

Historically, the U.S. Environmental Protection Agency (U.S. EPA) and a number of other government agencies have been interested in the use of human tissue

specimens and specimen banks for biological monitoring (14). The U.S. EPA first began serious discussion of plans and possible proposals for a National Environmental Specimen Banking System (NESBS) at a conference held in 1973 at the National Environmental Research Center in Research Triangle Park, North Carolina. The general objectives of the NESBS were to provide short-term specimen banking to study current trends in population body burdens of toxic pollutants and to provide long-term specimen banking for future retrospective studies of toxic exposures. In 1973 a workshop on the collection, long-term storage, and utility of environmental and biological specimens was sponsored by the National Academy of Sciences (NAS) and the National Research Council (NRC) at Capon Springs, West Virginia. Program objectives were refined and formally proposed at this workshop. These objectives were to survey and evaluate current specimen banking efforts, to evaluate the state of knowledge of sample preparation and storage methodologies, to evaluate future research needs, and to develop a planning document for the organization and management of a National Environmental Specimen Bank. In December of 1973, this proposal was jointly funded by the U.S. EPA, the National Bureau of Standards (NBS), and the National Science Foundation.

In 1975, the U.S. EPA and the NBS began a joint project to research and evaluate methodologies needed to actually put a National Environmental Specimen Bank into operation (15). Also in 1975, the United States and the Federal Republic of Germany signed an agreement to jointly research methodologies needed for the banking of environmental and biological specimens and to establish "pilot specimen banks" in both countries (16). These efforts led to the establishment of a Pilot Environmental Specimen Bank in West Germany in 1976 and in the United States in 1979.

From 1977 to 1982, review and evaluation of current research and ongoing specimen banking programs were carried out at three international workshops on biological monitoring, exposure assessment, and specimen banking (17-19). These workshops were jointly organized by the Commission of the European Communities, the U.S. EPA, the World Health Organization, the Federal Environmental Agency in West Berlin, and the Federal Ministry for Research and Technology in Bonn, Germany. In September of 1991, the U.S.

EPA and the German Ministry for the Environment, Nature Protection, and Reactor Safety cosponsored the First International Symposium on Biological Environmental Specimen Banking in Vienna. This symposium dealt with "Specimens, Sampling, Standardization, and Storage for Monitoring and Environmental Policy."

During this same period, there was also a second program of biological monitoring and human tissue specimen banking operating at the U.S. EPA (20). At the time of the U.S. EPA's creation in 1970, it inherited the National Human Monitoring Program (NHMP) from the U.S. Public Health Service. The NHMP had been founded in 1967 as a government program with the mission of conducting biological monitoring of human tissue specimens for environmental pollutants. One of the major activities of the NHMP was the National Human Adipose Tissue Survey (NHATS), which was intended to be a continuously operating survey that would collect, store, and analyze samples of autopsy and surgical specimens of human adipose tissue to be representative of the major metropolitan areas of the country. The NHATS was originally part of the U.S. EPA's Office of Pesticide Programs. In 1981, the NHATS was transferred to the U.S. EPA's Office of Toxic Substances and subsequently had its range of monitored environmental chemicals expanded from mainly pesticides to include other major classes of toxic chemicals. At that time the NHATS mission was redefined as being to identify toxic chemicals in human tissues, establish baseline data and trends, and to identify any population groups with unusually high toxic chemical exposures. However, during the 1980s, budget cuts decreased the activities of the NHMP to the point at which it consisted only of a moderately reduced version of the NHATS. The U.S. Congress decided to continue funding NHATS at this reduced level until 1990, when the National Research Council was scheduled to conduct a study of the design, needs, and utility of the NHMP. That study (20) concluded that a more comprehensive national program of human tissue monitoring was a critical need, not only for the U.S. EPA's mission to assess human exposures to environmental toxins and to better understand their health effects, but also for evaluating the needs and effectiveness of the U.S. EPA's regulatory programs. The study recommended that the NHMP and NHATS be completely redesigned to

provide more useful data based on probability samples of the whole U.S. population and that funding be increased to permit the programs to credibly fulfill their missions.

It was with this background and history that the present symposium was organized and held on 30 March to 1 April 1993 in Research Triangle Park, North Carolina. It was cosponsored by the University of North Carolina School of Public Health (UNC-SPH) and the Health Effects Research Laboratory (HERL) of the U.S. EPA. The Symposium Organizing Committee consisted of scientists from UNC-SPH (Barbara Hulka and Lester Lee), HERL (Jack Griffith and Richard Everson), the National Institute of Environmental Health Sciences (George Lucier), and the Centers for Disease Control and Prevention (Vernon Houk).

The symposium registered 117 participants from 18 states and five foreign countries and featured 21 invited speakers from several government agencies, including the U.S. EPA, the Centers for Disease Control and Prevention (CDC), and the National Institute of Environmental Health Sciences (NIEHS), and from universities in the United States, Canada, Germany, and Norway. The presentations and discussions by these invited speakers provided the basis for the 15 papers that follow this overview.

The objectives of this symposium were *a)* to provide a state-of-the-art overview of human exposure assessment techniques (especially applications of biological marker technology) and their uses in biological monitoring; *b)* to review advances in the design and implementation of human tissue specimen banking; and *c)* to synthesize and apply these techniques and advances to the development of tissue specimen banks well suited to future research needs in the areas of human exposure assessment, risk assessment, and environmental epidemiology. The symposium program was designed to approach these objectives initially from a theoretical perspective, followed by the more practical perspective of operating biological monitoring or specimen banking programs. The symposium program consisted of four sessions, each followed by a panel discussion with the symposium attendees. The first session began by addressing the opportunities that human tissue monitoring and specimen banking offer for research and public health practice in the areas of risk assessment, exposure assessment, and environmental epidemiology. The second session included four presentations on

biological monitoring and exposure assessment. The third session dealt with design and methodological issues, including sample design and analysis, specimen collection, bank management, and ethical issues. In the fourth session speakers presented applications and practical experiences of ongoing biological monitoring and specimen banking programs in the United States and Europe. Finally, after the last formal presentation of the symposium, a small workshop was held to specifically consider the role of specimen banking in the process of risk assessment.

### The Opportunities

The symposium opened with three presentations that addressed the utility and research opportunities afforded by biological markers used in biological monitoring and by specimen banking programs for present and future research needs in the areas of risk assessment (presented by Hal Zenick, HERL), human exposure assessment (presented by Ken Sexton, U.S. EPA), and environmental epidemiology in public health practice (presented by Lynn Goldman, currently at the U.S. EPA).

Dr. Zenick began his presentation with the observation that, while there is a multitude of biomarkers of exposure, effect, and susceptibility, the number which also meets stringent criteria of validation (21), proves to be practical in the field, and is suitable for banked specimens is somewhat small. Nevertheless, as this small number grows with continuing research, the utility of biomarkers to the risk assessment process also grows. The use of biomarkers of exposure in the exposure assessment process is obvious and biomarkers of effect may be useful in hazard identification, especially if these indicators can be detected at very low levels and are predictive of subsequent adverse health effects. Both types of biomarkers may be useful in dose-response estimations if there is sufficient understanding of the mechanistic (pharmacokinetic) link between the biomarker of exposure (indicative of dose) and the biomarker of effect (response). Biomarkers could also be particularly useful in making high-to-low dose extrapolations and in the study of interindividual variability.

Given the lessons learned from the shortcomings and design flaws of previous specimen banking efforts, careful definition of the target population and design of the sampling frame are essential for any specimen bank to be useful in risk assessment. For example, in this context, populations

that are either highly exposed or highly susceptible to adverse health effects of the exposure would be of particular interest. The utility of any specimen bank to the risk assessment process will usually be retrospective in that it could reaffirm biological significance, predictive value, or dose-response relationships of biomarkers when their values can be compared to follow-up exposure and health outcome data. Specimen banking may also provide historical baseline data for defined populations or help identify new high risk groups with increased exposure or susceptibility.

Opportunities for research in human exposure assessment were presented by Ken Sexton in the framework of the U.S. EPA's National Human Exposure Assessment Survey (NHEXAS). The goal of NHEXAS is to use measurements and models to estimate exposures and dosages of important environmental pollutants in representative samples of the whole U.S. population and certain highly exposed or highly susceptible subpopulations and to study causes and trends of exposure through time and space. These estimates are usually based on measurements of pollutants in the immediate or general environments of potentially exposed humans; models of exposure and dose based on contact with the pollutant and pathways of uptake; and pharmacokinetic models of the pollutant in the body. Biomarkers and biological monitoring offer the opportunity to independently study the relationship between exposure and dose and to compare biomarker measurements with estimates derived from the environmental measurements and models. Three questions were posed as opportunities or challenges for future research: *a)* How can human tissue monitoring and specimen banking be used to help us make better decisions? *b)* How important is human tissue monitoring and specimen banking compared to making environmental measurements of a pollutant? and *c)* How do we measure the success of specimen banking efforts?

Opportunities for the use of human tissue monitoring and specimen banking in environmental epidemiology and public health practice were discussed by Lynn Goldman in the context of ongoing public health studies and surveillance programs, such as cancer, birth defects, and asthma registries. Unsatisfied surveillance needs might well be addressed by the banking of human tissues. Specimen banking could be used for the monitoring of trends in population exposures, for the evaluation of the efficiency of environmental regulation, as a sentinel system for exposure to new

environmental pollutants, for the assessment of low level exposures near hazardous waste sites, and in nested case-control studies to investigate environmental etiologies of diseases such as childhood cancers and birth defects. California's Department of Health Services is involved in a number of studies using specimen banks in a study of childhood cancers and biomarkers in a surveillance system. An example of the latter is a serum  $\alpha$ -feto protein screening program that also evaluated serum subsamples for cotinine levels (measuring exposure to nicotine in tobacco smoke) for comparison to certain birth outcome variables. Finally, a number of ethical issues were raised such as the duty to provide culturally sensitive and accessible risk communications to study populations and individuals. There is also the issue of environmental equity and the likelihood of highly exposed individuals being poor, disenfranchised, and less educated. Not only does this circumstance make successful risk communication more challenging, but it also indicates that early community involvement in a study's design, planning, and execution is imperative.

### Biological Monitoring and Exposure Assessment

The second session focused on the use of biological measurements in groups of individuals or population samples to carry out exposure assessments. Paul Lioy (Environmental and Occupational Health Sciences Institute) began this session by comparing methods of measuring internal exposure biomarkers to methods measuring external markers of exposure such as personal monitoring devices, microenvironmental sampling, and activity pattern measurements. The need and possibilities of integrating these two personal monitoring approaches in exposure assessment were illustrated using studies of chromium in the house dust of people living near hazardous waste sites and studies of lead in the blood of inner-city children. This theme was continued in the discussion of several large studies done by James Pirkle using biological monitoring applications at the CDC. For example, the reduction in blood lead levels in the U.S. population between 1976 and 1980 closely paralleled the decline of lead in gasoline. Such a close relationship between biological and environmental lead levels was unexpected because the models that had been developed to predict the effect of reducing lead in gasoline had neglected a major route of human exposure to lead from gasoline—lead in environmental dust. Dr. Pirkle also discussed other studies where biological

monitoring data and banked human tissues convincingly validated or invalidated a variety of indirect methods of exposure assessment for dioxin and volatile organic compounds under various study conditions.

The use of biomarkers to assess dietary exposures in epidemiologic studies was discussed by Gerald Wogan (Massachusetts Institute of Technology). Using protein and DNA adducts of aflatoxin B<sub>1</sub>, a potent liver carcinogen, he was able to validate their use in assessing recent dietary exposure to aflatoxin in a study in Gambia. The same molecular biomarkers were used in China to study the interaction between aflatoxin exposure and chronic hepatitis B virus infection as risk factors for primary liver cancer. The study showed that the relative risk for liver cancer associated with aflatoxin exposure alone was 4.8 and that it rose to 60.1 for people with both aflatoxin exposure and chronic hepatitis B virus infection.

The last presentation of this session was given by Stephen Rappaport (UNC-SPH) on the relationship between environmental monitoring and biomarkers in exposure assessment. He argued for the importance of measuring intraindividual variation of biomarkers and comparing it to the corresponding variation in exposure experienced by the same individual. A regression of the subjects' mean biomarker values on their mean environmental exposures would describe the biomarker–exposure relationship. A large correlation coefficient would indicate linear pharmacokinetics, small differences between individuals, and adequate sample sizes of intraindividual measurements, a small correlation coefficient would indicate the opposite. He then described a study which found that personal exposure monitoring of the subjects' immediate environment was a better measure than a number of biomarkers for studying the dose–response relationship. The underlying reason for this was that the ratio of within-subject to between-subject variance was much larger for the biomarkers compared to the personal monitoring measurements.

### Design and Methodological Issues

With this session, the symposium began to turn to more practical issues of designing studies using biological monitoring or specimen banking. As mentioned above, a critically important design issue for any biological monitoring or specimen bank is the construction of its sampling design. Robert Murphy and Trena Ezzati-Rice,

both from the National Center for Health Statistics, started this session by drawing from their experience with the National Health and Nutrition Examination Surveys (NHANES). It is generally desirable to have a probability sample of the members of a defined target population in which every member of the target population (i.e., the potential sample universe) has a known probability not equal to zero of being sampled. Use of probability sampling methods is necessary for large-scale biological monitoring studies so that results can be used to infer quantitatively exposures or health effects from the probability sample to the target population. Another important sampling issue is that of oversampling special populations, such as minorities and highly exposed or highly susceptible groups.

Issues relating to choice of bankable tissues, intra- and interindividual variation, and temporal variation of exposure biomarkers were addressed by George Lucier and Claudia Thompson, both from NIEHS. Advances in the areas of molecular genetics and molecular epidemiology now make it possible to study genetic polymorphisms of the enzymes used to metabolize xenobiotic compounds, presymptomatic genetic changes (e.g., somatic mutations) associated with increased risk disease, and other genetic markers of susceptibility. The capability of studying the RNA species present in tissue samples permits researchers to study tissue-specific gene expression. Finally, the advent of new technologies, such as polymerase chain reaction (PCR), now makes it possible to detect specific genotypes and specific RNA species in extremely low concentrations. PCR technology alone greatly increases the potential of obtainable data from very small amounts of banked tissue of any type, as long as its preparation and preservation conditions are compatible with PCR analysis.

The specific issues and technologies concerning preparation and preservation of tissue specimens for archival storage in a specimen bank were presented by Elaine Gunter, Chief of the NHANES Laboratory at the National Center for Health Statistics. She addressed issues ranging from database management of the archived tissue and associated data about the subject who provided the specimen, to choice of storage container, type of freezer, and stability of analytes of possible interest. The same issues were examined by Stephen Wise of the National Institute of Standards and Technology (NIST) from the perspective

of quality assurance procedures used in operating tissue specimen banks at NIST.

The session concluded with ethical considerations raised by biomarker research and the collection of human tissues for specimen banks. Confidentiality issues, informed consent, the rights of human subjects, and the uses of monitoring data in research and regulation were presented and analyzed by Paul Schulte of the National Institute for Occupational Safety and Health and by Diane Wagener of the National Center for Health Statistics.

### Experiences with Biological Monitoring and Specimen Banking Programs

The fourth and final session of the symposium dealt with applications and practical experiences of ongoing biological monitoring and specimen banking programs in the United States and Europe. It opened with John Bailor of McGill University presenting a summary of his experiences chairing the National Academy of Sciences study of human tissue monitoring (20). Fritz Kemper of the University of Muenster gave an overview of the operations of the German Environmental Specimen Bank for Human Tissue in Muenster. Egil Jellum of the Norwegian Cancer Society described some of the history and research projects done at the JANUS Serum Bank in Norway.

A study of banked biologic specimens from about 1000 participants in NHANES III for the biological monitoring of 44 different environmental pollutants was presented by Larry Needham of the CDC. Biological monitoring of volatile organic compounds (VOCs) poses some special problems because of their rapid rate of loss from the body through exhaled breath. Lance Wallace of the U.S. EPA addressed recent advances in measuring exhaled breath and estimating exposure and body burden for VOCs in a study involving 800 subjects. Finally, Lenore Kohlmeier of the University of North Carolina School of

Public Health described a practical aspiration method for sampling adipose tissue from living subjects that had been successfully used in a 12-country study of myocardial infarction, breast cancer, and dietary antioxidants in Europe.

### Workshop on Specimen Banking and the Risk Assessment Process

The third day of the symposium consisted of a small workshop of about 20 people discussing the specific implications of the proceedings of the previous 2 days for the process of human risk assessment. The purpose of the workshop was to develop recommendations to the U.S. EPA regarding the application and utility of large scale specimen banking (i.e., biological monitoring and storage of tissue specimens) as it applies to the risk assessment process at the U.S. EPA, and other government agencies. The group discussed the establishment of a National Human Tissue Bank and the impact that such a bank would have on the following three elements of the risk assessment process: exposure assessment, hazard identification, and dose-response estimation. Among the group's major recommendations was one that the National Academy of Sciences should conduct a follow-up study to their 1991 study of human tissue monitoring (20). This new study would thoroughly investigate the objectives, design, and management of a National Human Tissue Bank. It was also recommended that the National Human Tissue Bank should be based on a national probability sample and that it be funded through a long-term, multiagency mechanism.

### Conclusions

Biological monitoring, exposure assessment, and health effects surveillance make up the critical parts of the empirical data base necessary to understand and evaluate the impact of environmental pollutants upon the public health. The hierarchical

goals of public health practice for the field of environmental health can be stated as: first, to prevent unacceptable toxic exposures from occurring in the first place; second, to reduce those toxic exposures that are judged to be unacceptable; and third, if the first two goals fail to be met, to identify and treat those whose health has been damaged by the toxic exposure (22). Thus, exposure assessment is the key measure for evaluating the success or failure of public health intervention programs for preventing environmentally related diseases and for establishing associations between particular toxic exposures and those suffering the adverse health effects that need to be identified and treated.

Human tissue specimen banking can play an important role in these endeavors. Biological monitoring in connection with specimen banking can serve a critical sentinel function for environmental toxic exposures by early identification of specific toxic hazards, before toxic effects on health become apparent. Applications of pharmacokinetic data can provide a basis for the biological interpretation of observed concentrations of various environmental toxins in body fluids and tissues.

Specimen banking may also serve a fundamental purpose in facilitating research to establish associations between particular toxic exposures and adverse health outcomes. Having banked tissue specimens available makes it possible to assay both biomarkers of exposure and biomarkers of health effects in the same specimens from the same individual. The ability to collect this type of data greatly facilitates research into establishing these associations. It also provides data that are potentially useful to the dose-response and exposure assessment activities of the risk assessment process. Finally, nested case-control study designs can be applied to banked specimens to investigate hypotheses concerning disease risk factors and early biomarkers of exposure biomarkers of subclinical disease as has been done in many human serum banks.

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### REFERENCES

- Zielhuis RL. General aspects of biological monitoring. In: *The Use of Biological Specimens for the Assessment of Human Exposure to Environmental Pollutants* (Berlin A, Wolff AH, Hasegawa Y, eds). The Hague: Martinus Nijhoff Publishers, 1979;341-359.
- Ott WR. Total human exposure. *Environ Sci Technol* 19:880-886 (1985).
- Liroy PJ. Assessing total human exposure to contaminants. A multidisciplinary approach. *Environ Sci Technol* 24:938-945 (1990).
- National Research Council. *Environmental Epidemiology: Public Health and Hazardous Wastes*. Washington: National Academy Press, 1991.
- Kutz FW, Strassman SC, Sperling JF. Survey of selected organochlorine pesticides in the general population of the United States: fiscal years 1970-1975. *Ann NY Acad Sci* 320:60-68 (1979).
- Strassman SC, Kutz FW. Trends of organochlorine pesticide residues in human tissues. In: *Toxicology of Halogenated Hydrocarbons: Health and Ecological Effects* (Khan MAQ,

- Stanton RH, eds). New York:Pergamon Press, 1981; 38–49.
7. Nisbet CT, Sarofin AF. Rates and routes of transport of PCBs in the environment. *Environ Health Perspect* 1:21–38 (1972).
  8. Drotman DP, Baxter PJ, Liddle JA, Brokopp CD, Skinner MD. Contamination of the food chain by polychlorinated biphenyls from a broken transformer. *Am J Public Health* 73:290–292 (1983).
  9. Schwartz PM, Jacobson SW, Fein G, Jacobson JL, Price HA. Lake Michigan fish consumption as a source of polychlorinated biphenyls in human cord serum, maternal serum, and milk. *Am J Public Health* 73:293–296 (1983).
  10. Lee RE. Environmental specimen banking. A complement to environmental monitoring. *Biol Trace Elem Res* 26-27:321–327 (1990).
  11. Hulka BS. Overview of biological markers. In: *Biological Markers in Epidemiology* (Hulka BS, Wilcosky TC, Griffith JD, eds). New York:Oxford University Press, 1990;3–15.
  12. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst* 85:648–652 (1993).
  13. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelmann J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J Natl Cancer Inst* 86:589–599 (1994).
  14. Goldstein G. The National Environmental Specimen Bank — its concepts, its history and its objectives. In: *The Use of Biological Specimens for the Assessment of Human Exposure to Environmental Pollutants* (Berlin A, Wolff AH, Hasegawa Y, eds). The Hague:Martinus Nijhoff Publishers, 1979; 165–176.
  15. Gills TE, Rook HL, Durst RA, eds. *The National Environmental Specimen Bank Research Program for Sampling, Storage, and Analysis*. Report no 600/1-79-017. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1979.
  16. Wise SA, Zeisler R. The pilot Environmental Specimen Bank program. *Environ Sci Technol* 18:302A–307A (1984).
  17. Berlin A, Wolff AH, Hasegawa Y, eds. *The Use of Biological Specimens for the Assessment of Human Exposure to Environmental Pollutants*. The Hague:Martinus Nijhoff Publishers, 1979.
  18. Luepke N-P, ed. *Monitoring Environmental Materials and Specimen Banking*. The Hague:Martinus Nijhoff Publishers, 1979.
  19. Lewis RA, Stein N, Lewis CW, eds. *Environmental Specimen Banking and Monitoring as Related to Banking*. The Hague:Martinus Nijhoff Publishers, 1983.
  20. National Research Council. *Monitoring Human Tissues for Toxic Substances*. Washington:National Academy Press, 1991.
  21. Schulte PA. A conceptual framework for the validation and use of biologic markers. *Environ Res* 48:129–144 (1989).
  22. Sexton K. Human exposure assessment and public health. *Prog Clin Biol Res* 372:455–466 (1991).