Human Biomonitoring: Research Goals and Needs

William A. Suk,1 Gwen Collman,1 and Terri Damstra2

1Division of Extramural Research and Training, National Institute of Environmental Health Sciences; 2National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

Epidemiological studies have taken advantage of a number of strategies to monitor human populations for mortality, incidence, and exposure to hazardous environmental agents. These studies have been compromised by the lack of individual exposure assessment data that precisely quantifies internal dose. As methods improve in analytical chemistry and molecular biology, direct biological monitoring of exposed populations has been developed and validated in exposed populations that quantify individual exposure, susceptibility, and early markers of health effects and can be used to study relationships between exposures and environmentally induced diseases. This paper provides background on the state of the art of human populations monitoring and, through a series of case studies, provides examples of novel biomarkers of exposure, susceptibility, and effect that highlight new opportunities for biomonitoring. Prevention of human disease due to environmental contaminants can be accomplished by implementing strategies such as those discussed to monitor exposures and early health effects in human populations. — Environ Health Perspect 104(Suppl 3):479-483 (1996)

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Introduction and Background

Epidemiological studies intended to evaluate the health significance of environmental agents are usually compromised by the lack of quantitative exposure data for individuals within exposed populations. Environmental monitoring data and estimates constructed by modeling often represent the only exposure information available; therefore, average population exposure is often used in studies of health effects. This method obviously is less precise in estimating health outcomes than using specific measurement of individual exposure doses in human effects studies.

Historically, epidemiological studies have taken advantage of a number of strategies to monitor human populations for disease occurrence and exposure to hazardous contaminants. As early as the 1800s, reviews of death certificates were used to describe the disease burden to populations and to attempt to attribute lifestyle factors or social ills to mortality. Communicable disease reporting is also an example of monitoring the population for a variety of contagious diseases. The Centers for Disease Control require physicians to report selected communicable diseases to monitor the levels of pathogens and viruses in the population. This reporting system is used to target susceptible subpopulations for immunization programs, to institute preventive programs such as rabies vaccinations, and to help identify new emerging microbes such as the hantavirus. Human population monitoring for chronic diseases is also widespread in developed countries. Scandinavian countries have developed a unique resource for human population monitoring by linking health insurance identification numbers, census data, and different hospital databases to create disease registries. Cancer and birth defect registries and other such surveillance systems have been used extensively in these countries to study trends of incidence, mortality, and health care utilization as well as to launch many noted epidemiological studies of disease etiology (1,2). In the United States, the SEER (Surveillance, Epidemiology, and End Results) network provides a geographically diverse set of population-based registries to monitor the occurrence of cancer across the United States. Many states have cancer and birth defects registries that vary in coverage and quality from hospital-based reporting to population surveillance.

Systems for monitoring the human population for exposures to environmental agents are not as well established. Federal agencies such as the U.S. Geological Survey and the U.S. Environmental Protection Agency routinely conduct environmental monitoring of air, water, and soils for a variety of pollutants (3). These environmental monitoring databases are beginning to be used in conjunction with health data to estimate human exposures from these media. Powerful new computer tools are available within geographic information systems for spatially linking the occurrence of disease cases with sources of contamination in diverse populations.

The Agency for Toxic Substances and Disease Registries (ATSDR) is mandated by Congress to conduct health surveillance programs of exposed populations. Many exposure registries have been compiled to facilitate this mandate. For example, surveillance of persons exposed to trichloroethylene, dioxin, benzene, and chromium has been established as part of the ATSDR National Exposure Registry. This surveillance includes health outcomes in seven priority areas: birth defects and reproductive disorders, cancer, immune function disorders, kidney dysfunction, liver dysfunction, lung and respiratory diseases, and neurotoxic disorders. Environmental monitoring data are reviewed at sites, mostly Superfund sites, to identify areas where exposure has taken place. Field studies are carried out to identify cohorts of exposed persons and enroll community residents. Registry participants are contacted periodically to provide updated information about health status (4).
Exposure Assessment
Assessing human exposure to chemicals, especially from Superfund sites, requires not only understanding and applying knowledge from a number of scientific disciplines but also the gathering of large amounts of data (5). It is necessary to know how chemicals behave once they have been deposited in these sites, how they behave once they are released from the sites, and how they behave once they come into contact with humans. This complex array of information must be gathered for a large variety of different chemicals and for human populations that vary significantly in important characteristics. Considering the importance of local conditions, assessments for each site must be location specific and so must depend on emission, transport, and exposure data gathered at that particular site using the population at greatest risk.

To characterize this complex situation, generic models are being developed that approximate the physicochemical behavior of chemicals and thus describe their environmental distribution and fate. Furthermore, physiological pharmacokinetic models developed in laboratory studies of experimental animals and clinical investigations of humans are being applied to environmental chemicals, concentrations, and routes of exposure in humans. Use of such information in human biomonitoring is necessary to estimate exposure, including a better understanding of human variability.

Molecular Biomarkers
As methods improve in analytical chemistry and molecular biology, direct biological monitoring of exposed populations is possible. Biomonitoring involves the use of biological or molecular markers as indicators signaling events in individuals exposed to environmental chemicals. Therefore, biological monitoring (i.e., acquisition of exposure data through analysis of cells, tissues, or body fluids of exposed people) may lead to identification of potentially hazardous exposures before adverse health effects appear and to establish exposure limits for minimizing the likelihood of significant health risks.

A number of techniques have been developed for monitoring human exposure to environmental or occupational carcinogens. Among these methods are the measurement of the chemical itself or its metabolites in body fluids (e.g., serum or urine) or the chemical bound to cellular macromolecules including DNA and protein, measurement of mutagens in urine, and measurement of early biological effects such as sister chromatid exchange and chromosomal aberrations. The following sections provide some case studies of biomonitoring using state-of-the-art molecular biology techniques that are available and have been validated for use in environmental epidemiology studies.

DNA Adducts
Detecting carcinogen DNA adducts is important in exposure monitoring and identification of early lesions in the development of cancer. Ultrasensitive and highly specific methods for measuring the DNA adducts associated with exposure to hazardous chemicals, such as the known human carcinogen vinyl chloride, have been developed by Froment et al. (6). Major advances have been made in the application of gas chromatography/high resolution mass spectrometry to the identification and quantification of V2,3-ethenoguanine (EG), the major promutagenic DNA adduct of vinyl chloride. Routine measurements of low femtomolar quantities of EG can now be made, and researchers have detected endogenous EG adducts in DNA from both human and animal liver samples (7).

Immunohistochemical techniques have been developed using monoclonal antibodies that recognize adducts to aflatoxin B1 (AFB1) (8). AFB1, a potent liver carcinogen in animals, has been associated with increased incidence of hepatocellular carcinoma in Africa and Southeast Asia, especially in the presence of hepatitis infection. To better understand the role of AFB1 exposure in human cancer incidence, biological monitoring methods have been developed to quantitate exposure on an individual basis (9). It is now possible to measure levels of the covalent adducts of AFB1 on DNA and protein quickly and effectively. Such measurements provide more meaningful information on exposure and, ultimately, on risk of cancer development.

Protein Adducts
Investigations into the utility of detection and quantification of adducts formed between environmental carcinogens and the blood protein hemoglobin as a means of monitoring carcinogen exposure have resulted in several important findings. The widely disseminated carcinogen 4-aminobiphenyl is an important component of cigarette smoke and is therefore encountered not only by smokers but also by nonsmokers through passive exposure to environmental tobacco smoke. Studies have revealed that levels of hemoglobin adducts of 4-aminobiphenyl accurately and quantitatively reflect levels of exposure in both smokers and nonsmokers (10). Adduct levels also decline in a predictable manner upon cessation of smoking. Importantly, in studies of smokers using different types of tobacco, adduct levels clearly reflected metabolic capability for metabolizing the compound in a manner that also correlated with elevated risk of bladder cancer. Further, studies of newborn infants of smoking and nonsmoking mothers revealed the presence of 4-aminobiphenyl adducts in hemoglobin of the infants at levels reflective of the exposure history of the mothers. Thus, this approach provides a sensitive and accurate means of monitoring prenatal exposure to maternal smoking metabolites and demonstrates the technique's potential to monitor exposures to a wide variety of carcinogens.

Mutational Spectra
Analytical genetics is a component of genetic toxicology, which applies biotechnology to the molecular events of mutagenesis. Understanding the mutational spectra of each chemical or physical exposure (the specificity and DNA context of a collection of mutations) is equivalent to identifying fingerprints that can in turn be used to identify the exposed populations. A novel combination of technologies has been developed that would allow the detection and characterization of mutation in an exposed population without the need for either phenotypic selection, which limits the number of detectable sites, or DNA sequencing, which is extremely time consuming. The principles of the new approach developed by Coller and Thilly (11) involve high fidelity polymerase chain reaction (HiFi-PCR) and denaturing gradient gel electrophoresis (DGGE). Together, these techniques permit the production of a mutational profile that can be expected to be unique for each agent. The advantages provided by the combined HiFi-PCR/DGGE are a) the potential for automation, b) a need for only a small cell sample, c) the potential to use any DNA target without the need for a phenotypic consequence, and d) this approach presents the possibility of screening populations rather than a few individuals.

Efforts are under way to improve on the HiFi-PCR/DGGE assay by developing an efficient and accurate PCR technology and refining the DGGE technology. This research will provide an improved approach
to detect mutations in exposed populations. For example, research on a specific gene sequence of human lymphocyte cells has demonstrated the applicability of these kinds of studies to human cell lines. In vitro, Mutational spectra for known environmental agents, including UV light and benz(a)pyrene diol epoxide (BPDE), as well as other known mutagenic agents (MNNG, ICR-191) and chromium have been produced. In a study of aflatoxin-exposed individuals in China, 2 mutational analyses of the hprt gene have shown mutants that have single-base substitutions occurring primarily at GC base pairs (14). In vitro work in the same study identified one strong mutational hotspot in exon 3.

**DNA–Protein Cross-linking**

Investigators have been attempting to understand DNA–protein cross-linking by metals and their role in carcinogenesis. Besides being a promising biomarker of exposure, DNA–protein cross-linking is a major form of genetic damage, one that persists during cell proliferation. In investigating the induction of this biomarker by metals, investigators have identified the structural protein actin as a major protein cross-linked to the DNA by these agents. Actin is also a major protein cross-linked to the DNA by several other cross-linking agents including UV light and cisplatin, a cancer chemotherapeutic agent. New studies have been performed with chromium and nickel, and DNA–protein cross-links are one of the primary lesions induced in cells exposed to these metals. Because actin is known to be important in the attachment of DNA to the nuclear matrix, in sites for DNA replication, and in the activation of transcription, these studies may lead to new insights into the mechanism of toxicity and carcinogenicity of metals as well as to other opportunities for biomonitoring DNA–protein cross-linking chemicals.

Costa et al. (15–17) have evaluated the feasibility of using the DNA–protein cross-link assay in peripheral white blood cells (WBC) to detect human exposure to both chromium and nickel compounds in occupational environments, specifically in welders. Their results demonstrate that welders have an elevation in this biomarker related to chromium and nickel exposure in the WBC and that the presence of this lesion in the WBC signals its probable presence in other tissues as well, e.g., the lungs, which presumably receive considerably higher exposure than the peripheral blood cells. The biomonitoring of residents living in chromium-contaminated areas of Hudson County, New Jersey, have also found a high degree of DNA–protein cross-linking in WBCs. Their results indicate that chromate exposure has occurred in these residents; there is concern regarding the high exposure to chromium and also the long-term health effects of this exposure.

**Monitoring of Exposed Cohorts**

**Air Pollution**

There is evidence of a link between environmental air pollution and cancer-related genetic damage in humans. Perera et al. (18) looked at mothers and their offspring in an industrial area having nonoccupational exposure to community air pollution. The researchers studied two population groups in Poland with differing degrees of exposure to air pollution from coal combustion. The highly exposed group lived in the town of Gliswile, Upper Silesia, an industrialized region characterized by high rates of cancer. The 49 unexposed controls were from Biala Podlaska, a rural province with roughly 10-fold lower levels of air pollution than in Gliswile.

An array of biological markers of molecular and genetic damage, indicators that signal events in individuals exposed to environmental chemicals, including DNA adducts, chromosomal mutations, and activation of ras oncogene, was measured. Perera et al. (18) found considerably higher levels of DNA and chromosomal damage in the exposed population compared to the control population. A doubling in the frequency of ras oncogene activation also occurred in the exposed group. This indicates that exposure to a complex mixture of pollutants was related to molecular and genetic damage in peripheral blood samples. Prior studies have linked these biomarkers to increased risk of cancer. Chromosomal mutations and carcinogen–DNA adducts are also highly relevant to reproductive damage. The results of this investigation showed statistically significant increases in all of the biomarkers in the exposed group compared to the controls. A relationship was observed between DNA adducts and structural alterations in the chromosomes. These studies provide a molecular link between environmental exposure and a genetic alteration relevant to cancer and reproductive risk. Ascertainment of molecular biomarkers in these cohorts at an early age provides a baseline set of parameters that can be monitored as the study subjects age.

**Polychlorinated Biphenyls**

Advances in analytical chemistry have created methods that detect smaller levels of toxicants in smaller volumes of body fluids and tissues. This is especially important because environmental epidemiology studies can be conducted as new hypotheses and technologies emerge by analyzing frozen specimens maintained in repository. In the past, measurements of dioxins in serum required nearly 100 ml to detect levels in the part-per-billion range; now part-per-trillion levels can be detected in samples of less than 10 ml (L.L. Needham, personal communication).

Cohort studies of children exposed to polychlorinated biphenyls (PCBs) in utero and in early life primarily through breast-feeding have indicated perturbations in growth and development (19). Monitoring of human milk specimens has provided estimates of the prevalence of organochlorine exposures due to the lipophilic nature and biopersistence of the chemicals (20).

Currently, the detection of the PCBs requires blood volumes in excess of 20 ml and thus necessitates venipuncture. This procedure is invasive, especially for infants and small children. A method has been developed by researchers that extracts the urine of infants from specially prepared cloth diapers and analyzes it for PCB congeners at the parts-per-trillion level. In a pilot study of five nursing infants, each had detectable levels of PCBs in the urine, and a significant correlation (r = 0.99) was observed between urinary PCB concentration and duration of breast-feeding. The method remains experimental, with further refinement and field testing under way. It may potentially enhance the opportunity to biologically monitor infants and small children, subgroups who are particularly vulnerable to the effects of PCBs (E. F. Fitzgerald, personal communication; 21).

**Genetic Susceptibility**

Studies at the molecular level in humans suggest that there is wide interindividual variability, consistent with the observation that disease risk is also highly variable among individuals. Yet, in most cases, risk assessment and subsequent regulation of disease-causing chemicals are based on the assumption that the general population is homogeneous in its response. Therefore, improved understanding of the nature and significance of human variation in
susceptibility and response has been termed a priority environmentally induced disease prevention. One of the goals of the National Institute of Environmental Health Sciences (NIEHS) is to attain a better understanding of inter- and intra-individual variability pertaining to the susceptibility of the human health effects to environmental chemicals.

For a small percentage of persons who develop cancer (less than 5%), inheritance of a defective gene significantly increases the risk for developing cancer. It is estimated that 1 in 10 women will develop breast cancer over the course of her lifetime. Although several etiologic risk factors have been identified for breast cancer, women who have inherited a mutated copy of the BRCA1 gene have approximately an 80% chance for developing breast or ovarian cancer. Colon cancer affects 1 in 200, but only for a small percentage of the population is there an inherited predisposition for developing this cancer. The activation of several oncogenes is necessary to initiate tumors, but for those individuals who inherited the colon cancer gene, a defect in the system to repair DNA allows for random mutations to occur in oncogenes.

In the general population, it has been observed that there are large interindividual variations in a person's ability to respond to DNA-damaging agents. Researchers have noted greater than 5-fold variations in excision repair in the general population; among individuals who had a history of cancer among first degree relatives, there was a significant reduction in unscheduled DNA synthesis compared to individuals with no family history of cancer. In addition, interindividual variation in the activity of O6-alkyguanine-DNA-methyl transferase, an enzyme important in the removal of O6-deoxyguanine has been noted. The significance of these population differences in repair enzyme activities in relation to chemical exposure and cancer risk is yet to be determined.

Perhaps the greatest advances in using molecular tools to unravel gene-environment interactions have been in studying the associations between exposure, polymorphisms in carcinogen-metabolizing genes, and cancer risk. The enzymes involved in carcinogen-metabolism fall into two broad categories: Phase I enzymes, which almost exclusively involve the cytochrome P450 gene superfamily but also include N-acetyl transferase and are involved in metabolic activation, and Phase II enzymes such as glutathione S-transferases (GSTs), which are involved in detoxification reactions and are considered protective pathways. Recent advances in molecular DNA techniques have allowed for the identification of polymorphisms at the genetic level for several enzymes important in carcinogen metabolism.

Bell et al. (23) have studied the associations between cigarette smoking, bladder cancer, and the glutathione S-transferase M1 (GSTM1) gene, which is polymorphic in the population and absent in approximately one-half of the Caucasian population. Their findings showed that persons who smoked and had no GSTM1 were at greater risk for developing bladder cancer than those individuals who smoked and were GSTM1 positive.

In an effort to combine molecular epidemiology and risk assessment, a number of investigators are pursuing the molecular characterization of genetic susceptibility of the human cytochrome P450 system as a potential biomonitor of chemical exposure and risk due to chemical exposure. A broad array of P450 genes has been characterized in both humans and animals; consequent to chemical exposures, these genes undergo changes in expression level or pattern in a variety of cell types. Genetic polymorphism in P450 expression may be an important determinant in differences in an individual's response to potential toxic exposures. Novel strategies have recently been developed for the specific and highly sensitive detection of P450 gene expression in a variety of human cells in culture and in primary cells isolated directly from human volunteers. These powerful assays, using PCR-based technology (24) and laser-activated fluorescence (25), that allow for the detection of P450-mediated enzymatic activities directly within individual cells should provide expanded use of the cytochrome P450 system as a biomarker of chemical effect in humans exposed to xenobiotic agents.

Studies at the molecular level in humans suggest that there is wide interindividual variability in genetic parameters and host characteristics which are consistent with observations that disease risk is also highly variable among segments of the population. Yet in most cases, risk assessment and subsequent regulation of disease-causing chemicals are based on the assumption that the general population is homogeneous in its response. Success in the prevention of morbidity from environmentally induced diseases relies on the ability to identify susceptible subgroups of the population and target effective intervention and prevention strategies to them. Therefore, improved understanding of the nature and significance of human variation in susceptibility and response is a priority of environmentally induced disease prevention.

Concluding Remarks and Research Needs

There has been marked progress during the past decade or so in the development of techniques for biomonitoring in environmental health sciences research. The initial enthusiasm created by technological advances has become tempered by the recognition of methodological issues and clarification of the role of biomarkers in etiological research. The indisputable strength of existing biomarkers lies in their sensitivity to low biologically effective doses of toxicant and their feasibility as indicators of molecular host response. Conversely, their limitations are related to the process of measurement.

Susceptibility factors can come into play at almost any point between exposure and disease outcome. Certainly differences in individual absorption, distribution, metabolism, and repair all have the potential to influence individual sensitivity to a particular environmental agent. In turn, these specific differences may account for the wide variations in incidence of disease between and within groups of people. Some of the most encouraging progress in this area has been in the development of biological markers of metabolism and of DNA repair. The objective of these studies should be to help elucidate the nature and significance of inter- and intrasubject variability in response to environmental agents. Furthermore, such investigations are an essential prerequisite to incorporating biological markers into quantitative risk assessment and epidemiological studies of environmentally induced disease causation.

Methodological concerns such as reproducibility, intra- and interlaboratory variability, intra- and interindividual variability, source and exposure specificity, and use of surrogate tissues are being addressed by independent and collaborative laboratories and investigators. Although the laboratory component is important, epidemiological study designs should account for background exposures and confounding variables. Combining measurements of dose or response (DNA and protein adducts) with markers of susceptibility may be a way of minimizing interindividual variability.
It is obvious that there is a need to validate existing and promising biomarkers in tissues, individuals, and populations. A concerted effort should be focused on assessing inter- and intraindividual variability as well as inter- and intralaboratory variability (26). Selection of laboratory measurement should be based on relevance to the end point and to the research hypothesis. Epidemiological study designs that incorporate biomarkers must take into account the methodological issues unique to their application. The future of biomonitoring human populations for disease and exposures lies in the discovery of new genes for chronic diseases and in the development of new biomarkers of exposure and susceptibility. The role of specimen repositories and laboratory networks is critical, and a mechanism of networking and funding mechanisms for such should be developed (27). Researchers conducting studies of exposed individuals should bank any unused blood, urine, tissues, and cells for the promise of future discoveries. It is therefore very important that future research encourage cooperation, collaboration, and communication between multidisciplinary research teams (28). To facilitate this process, regular interdisciplinary conferences could encourage interactions, improve the understanding of technical and logistic problems, and clarify data interpretation.

Prevention of human disease due to environmental contaminants can be accomplished by implementing strategies to monitor exposures and early health effects in human populations. New technologies entwined with diligent surveillance offer promise of further understanding of the role of environmental exposure in human disease.

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