Environmental Health Perspectives
Vol. 74, pp. 3-9, 1987

Biological Markers in Environmental Health Research

by the Committee on Biological Markers of the National Research Council*

The National Academy of Sciences/National Research Council (NAS/NRC) was asked by the Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences to conduct a study of the scientific basis, current state of development, validation, and use of biological markers in environmental health research. The project is being conducted by four subcommittees of the Committee on Biological Markers within NRC's Board of Environmental Studies and Toxicology. These groups will evaluate the status of biological markers for specific biological systems: markers of reproductive and developmental effects, with an emphasis on neurodevelopmental effects; pulmonary system markers of exposure, effects, and susceptibilities; markers of immunological changes as they relate to cancer, including childhood cancer; and markers of ecological toxicity, including markers of ecosystem exposure and altered processes.

As part of this project, the Subcommittee on Reproductive and Developmental Toxicology convened a symposium January 12–13, 1987, in Washington, DC. Invited speakers described their research and its possible application to the development and use of biological markers. This issue of *Environmental Health Perspectives* contains the proceedings of that symposium.

In this introductory article, the parent committee sets forth in general terms the broad concepts and definitions of biological markers and discusses the use of markers in environmental health research. The committee's deliberations are continuing; the following is offered as an introduction to the symposium and as an indication of the kinds of information and concepts being used by the committee. An extended report from the Committee on Biological Markers and its Subcommittee on Reproductive and Developmental Toxicology is in preparation and will be published separately by the National Academy Press and will contain the findings and conclusions of the committee.

Concepts and Definitions

Biological markers are indicators signaling events in biological systems or samples. It is useful to classify biological markers into three types, those of exposure, effect, and susceptibility, and to describe the events particular to each type. A biological marker of effect may be an indicator of an endogenous component of the biological system, a measure of the functional capacity of the system, or an altered state of the system that is recognized as impairment or disease. A biological marker of susceptibility is defined as an indicator that the health of the system is especially sensitive to the challenge of exposure to a xenobiotic compound (a compound originating outside the organism). A biological marker of exposure may be the identification of an exogenous substance within the system, the interactive product between a xenobiotic compound and endogenous components, or other event in the biological system related to the exposure. Of utmost importance is the correlation of biological markers of exposure with health impairment or potential health impairment.

It must be emphasized that there is a continuum between markers of exposure and markers of health status, with certain events being relatable to both types of markers. The terms biological monitoring and health monitoring are also in common use, and their distinguishing features are subject to debate (*1*). In essence, biological markers can be used for both biological monitoring and health monitoring.

Once exposure has occurred, a continuum of biological events may be detected. These events may serve as markers of the initial exposure, internal dose, biologically effective dose (dose at the site of toxic action, dose

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at the receptor site, or dose to target macromolecules), altered structure/function with no subsequent pathology, or potential or actual health impairment (Fig. 1). Even before exposure occurs, there may be biological differences between humans that cause some individuals to be more susceptible to environmentally induced disease. Biological markers, therefore, are tools that can be used to clarify the relationship, if any, between exposure to a xenobiotic compound and health impairment.

Markers of Exposure

External exposure is the sum of the xenobiotic material presented to an organism, whereas internal dose is the amount of the xenobiotic compound that is actually absorbed into the organism. Biological markers of internal dose may include pharmacokinetic data, such as half-life, circulating peak, or cumulative dose. Biologically effective dose is the amount of material interacting with critical subcellular, cellular, and tissue targets or with an established surrogate.

Several factors should be considered before making qualitative or quantitative estimates of exposures. For example, the concentration, duration of exposure, and physicochemical nature of the toxicant are all relevant to the selection of an appropriate marker of exposure. The physicochemical properties of the xenobiotic substance and its stability in the environment or matrix in which it occurs influence exposure and accuracy of exposure monitoring (*2*).

Differences among species and individual variations in physiological characteristics such as sex, age, and health status can significantly affect the absorption and distribution of the chemical and its metabolites. Individual response to environmental temperature, such as the ingestion of large quantities of water, also may affect absorbed dose. Diet or hormonal status can alter gut motility and gastric emptying time, which in turn influence absorption by changing residence time in the small intestine or stomach, respectively.

Blood flow, capillary permeability, transport into an organ or tissue, the number of receptor sites, and route of administration (which determines the path of the parent compound or its metabolites in the body) can all influence internal or biologically effective dose. Figure 2 is a general model showing the relevant body compartments for a variety of routes of administration. An inhaled carcinogen might produce tumors in the lung, but if the same material were ingested and eliminated via the kidney, renal tumors might be produced. If the parent compound is responsible for the observed toxicity, the amount of metabolite reaching the target may be of no consequence. If metabolites are responsible, however, metabolism in the liver, the target organ, or elsewhere as a result of metabolic cooperation between several tissues is an important determinant of internal and biologically effective dose.

Exposure to environmental agents has classically been assessed by mathematical modeling based upon assumptions concerning emission sources, environmental fate, and the location of individuals in space and time. Exposure has also been assessed by ambient monitoring using chemical or physical analyses of food, air, water, or soil, coupled with measurement or estimation of actual human intake of these media, and by biological markers of exposure including measurements in body fluids such as blood, urine, saliva, cerebral spinal fluid or, for reproductive and developmental systems, follicular fluids, amniotic fluids and cells, and semen. Examination of other biological samples, such as hair, feces, or teeth, may prove useful. The use of such biological markers is a more preferable means for accurately estimating exposure than are the more indirect approaches of modeling or ambient monitoring.

Markers of Effect

For present purposes, the effects on, or responses of, an organism to an exposure are considered in the context of the relationship of exposure to health impairment or the probability of health impairment. An effect is defined as: an actual health impairment or (by general consensus) recognized disease; an early precursor of a disease process that indicates a potential for impairment of health; or an event peripheral to any disease process but correlated with it and thus predictive of development of impaired health.

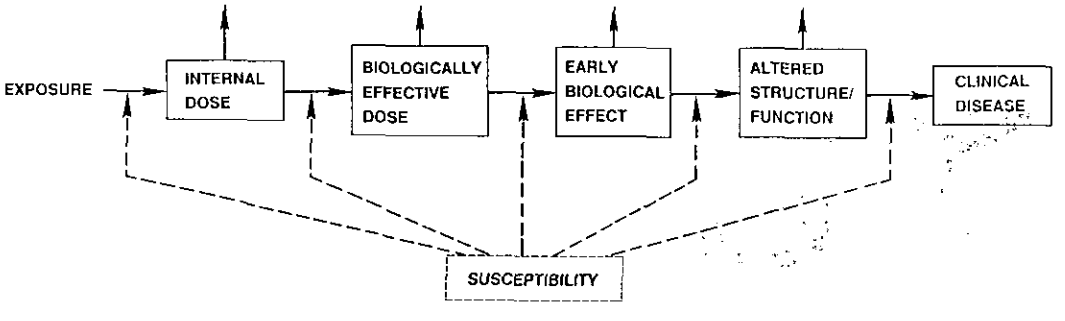

FIGURE 1. Simplified flow chart of classes of biological markers (indicated by boxes). Solid arrows indicate progression, if it occurs, to the next class of marker. Dashed arrows indicate that individual susceptibility influences the rates of progression, as do other variables described in the text. Biological markers represent a continuum of changes, and the classification of change may not always be distinct.

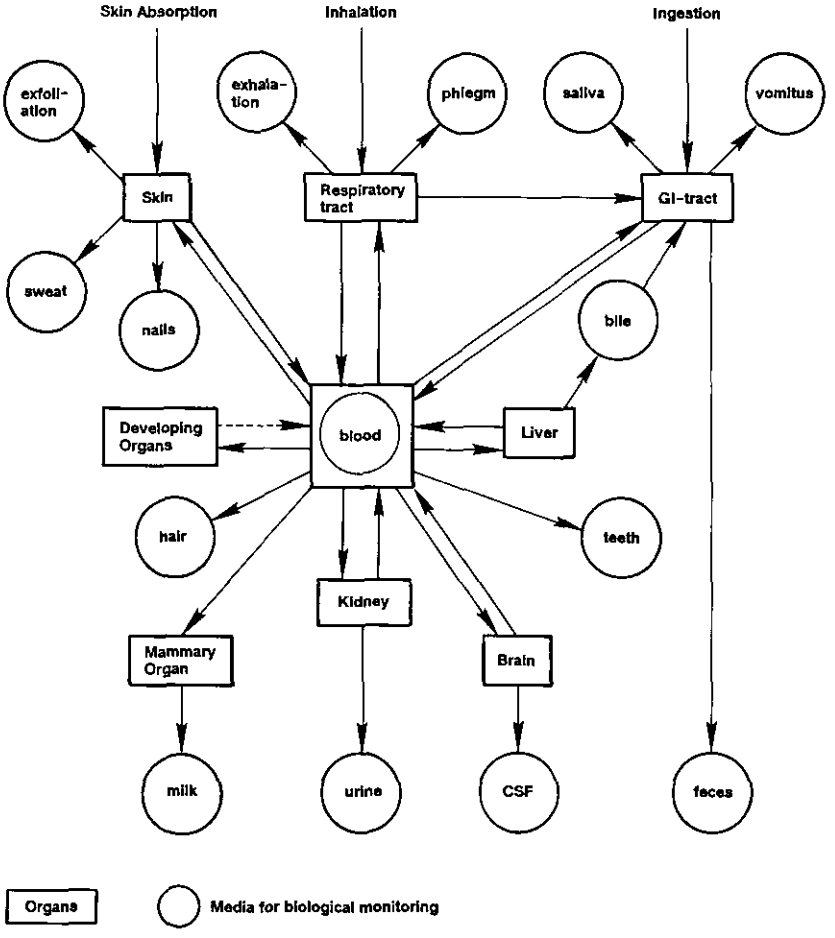

FIGURE 2. A general model showing the possible metabolic pathways of a xenobiotic compound by three routes of exposure and their association with target tissue dose. CSF, cerebral spinal fluid. Adapted from Elinder et al. (*1*).

A biological marker of an effect or response, then, can be any change that is qualitatively or quantitatively predictive of health impairment or potential impairment resulting from exposure. Biological markers are also useful to identify an endogenous component or a system function that (by general consensus) is considered to signify "normal" health, e.g., blood glucose. It is important to realize, however, that these markers represent points on a continuum whose boundaries may change as knowledge increases.

Early biological responses may include alterations in the functions of the target tissue shortly after exposure. Organs or tissues that are not directly involved in the disease process may also exhibit a response proportional to the biologically effective dose. These responses, such as lymphocyte sister chromatid exchanges (SCEs) or red cell δ-aminolevulinic acid dehydratase (ALAD) activity, may be thought of as surrogates for the response occurring in the target tissue and could thus be used as markers of response at the site of action. An example of a marker that is closely related to external dose, biologically effective dose, and health status is carboxyhemoglobin (COHb) (*3*). Unfortunately, markers of health effects are often less readily related to environmental exposures than are the markers of exposure described above.

Later in the course of the response to the xenobiotic compound, or after an internal dose reaches a sufficient duration or intensity, the affected tissue will exhibit altered function—a response that may be a subclinical manifestation of disease. Biological markers useful at this stage are likely to be related to the affected organ or system, for example, organ-specific markers as determined by biochemical analyses. When the biologically effective dose reaching the target tissue is sufficient to alter function irreversibly, overt disease may develop. Disease characteristics (e.g., acute neurotoxic, adverse cardiopulmonary, testicular, ovarian, fetal, or placental effects) occurring shortly after an exposure may be directly linked to the xenobiotic compound. However, it may be difficult to relate disease (e.g., ovarian or testicular failure) to an exposure distant in time unless the disease has characteristics or biological consequences (e.g., mesothelioma or chloracne) specific to a certain type of exposure. Most biological markers used to describe the disease state will be specific to the dis-

eased organ or system and may have little relationship to the xenobiotic compound that initiated the disease process. For environmental health research, the most useful biological markers will be those that can be attributed to a specific environmental exposure.

Markers of Susceptibility

Some biological markers indicate individual or population differences that affect response to environmental agents independent of the exposure under study. An intrinsic genetic or other characteristic or a preexisting disease that results in an increase in the internal dose, the biologically effective dose, or the target tissue response can be markers of increased susceptibility (*4*). Such markers may include inborn differences in metabolism, variations in immunoglobulin levels, low organ reserve capacity, or other identifiable genetically determined or environmentally induced variations in absorption, metabolism, and response to environmental agents. Other factors that may affect individual susceptibilities include nutritional status of the organism, the role of the target site in overall body function, condition of the target tissue (present or prior disease), and compensation by homeostatic mechanisms during and after exposure (*5*). The reserve capacity of an organ to recover from an insult at the time of exposure may also play an important role in determining the extent of an impairment.

Selection of Biological Markers

Ideally, a biological marker of exposure should vary consistently and quantitatively with the extent of exposure (especially at low doses) and should be specific for the environmental exposure of concern. Specific markers of exposure include the presence of a xenobiotic compound or its metabolites in body tissues or fluids and in excretory products. Blood and urine are the most commonly analyzed. For example, exposure to mercury, lead, or arsenic can be confirmed by the presence of the metal in urine; the determination of *p*-nitrophenol in urine is used as an indicator of exposure to parathion, and the presence of chlorinated pesticides and polychlorinated biphenyls in adipose tissue is used as a marker of exposure to these lipophilic chemicals.

Other biological markers may reflect a particular change that is characteristic of exposure to specific xenobiotic compounds. Examples include the reduction of acetylcholinesterase activity in the plasma of persons exposed to organic phosphate insecticides (*6*) and the appearance of δ-aminolevulinic acid in the urine of those exposed to lead (*7*). Nonspecific markers can also be useful, particularly if they can be related to environmental exposure. For example, serum α-fetoprotein (AFP) has been used in China as a biological marker for preneoplasia of the liver, which is common in that country. The production of AFP has been found to be proportional to the tumor load (*8*). In addition, high levels of AFP in maternal serum suggest a fetal neural tube defect (*9*), and low levels of AFP are associated with fetal karyotypic abnormalities (*10,11*). Accordingly, AFP is a nonspecific marker of health status. Its value for environmental health research would be in studies exploring the relationship of these disease entities to exposure.

A mechanistic approach to understanding the basic events resulting in an adverse health effect can be applied to the selection of an appropriate biological marker. This is best demonstrated in research on carcinogenesis. Many carcinogens have been shown to be mutagenic or otherwise damaging to DNA. Therefore, much research has been directed toward developing short-term assays for genetic toxicity, such as the Ames Salmonella mutation assay and tissue-culture assays for determining chromosomal aberrations or increased incidence of SCEs. These assays have been adapted to assess human exposure to potential carcinogens. For example, the Salmonella assay has been used to ascertain mutagenic activity in urine from persons exposed to mutagenic chemicals, e.g., by smoking cigarettes, by working with industrial chemicals, or as a result of treatment with cytostatic chemotherapeutic drugs (*12*). The frequency of chromosomal aberrations and, more recently, lymphocyte SCEs has been used to assess human exposure to genotoxic agents, both physical (i.e., radiation) and chemical (*13*). Techniques based on specific monoclonal and polyclonal antibodies, fluorescence spectrophotometry, thin-layer chromatography, and gas chromatography have been used to detect DNA adducts resulting from exposure to mutagens and carcinogens (*14*).

Validation of Biological Markers

It is essential to validate the use of a biological change as an environmentally induced marker by establishing that a relationship exists between an exposure and the biological change of interest. One useful approach is to develop a matrix of information from experimental studies in animals and clinical studies in humans that enables one to make estimates for humans (Table 1). Markers of acute effects for short-term, low-level exposures to a pollutant can be determined in both animals and humans. A comparison of this information with markers

Table 1. Example of a matrix for determining the validity of a biomarker.

Species	Nature of exposure	External exposure	Internal dose	Health effect
A	Acute	X	X	X
	Chronic	X	X	X
B	Acute	X	—	X
	Chronic	—	—	—
Human	Acute	X	X	X
	Chronic	?	?	?

X = Marker determined.
— = Marker not yet determined.
? = Not yet tested.

for chronic effects resulting from the long-term exposure of animals to the same pollutant could lead to the development of markers that are predictive of health effects in chronically exposed humans.

Quality Control

In addition to selection and validation, the development of adequate laboratory procedures for application of suitable tests to measure markers is fundamental to the assurance of accurate, objective, and verifiable findings. Most tests of quality assurance are statistical, based on an assumption of a Gaussian distribution of measurements (*15,16*), but some criteria for quality assurance transcend statistical criteria. They may involve considerations of sensitivity, instrument design, and methodology, as well as limitations on the applicability of tests in circumstances where the expected result may not be different from background levels (*17*).

General issues of quality assurance and quality control have been addressed by the EPA (*18–20*), the Food and Drug Administration (FDA) (*21*), the Organization for Economic Cooperation and Development (*22*), and other regulatory organizations (*23–27*). The FDA guidelines for good laboratory practice (GLP) (*18*) are now incorporated into the standard procedures of most testing and analytic laboratories and are intended to reduce the chance of contamination or changes in biological variables introduced by sample storage, processing, or measurement (*28*). Contamination is an important concern when measuring markers of exposure. The application of GLP goals to the analysis of biological samples, especially human tissue, has been considered by operational units within the Centers for Disease Control, the National Bureau of Standards, and various clinical laboratories (*15–17,24–25*).

Use of Biological Markers in Environmental Health Research

Biological markers are powerful tools that can be used to address many different issues confronting environmental health scientists. Markers that indicate the occurrence of an internal dose, a biologically effective dose, or the presence of an incipient disease can be useful in hazard identification, for example, as the qualitative step that causally associates an environmental agent with an adverse effect (*29*). Markers can also be used to determine dose-response relationships and to estimate risk, especially at the low doses relevant to most environmental chemicals. Thus, the development of biological markers may enable scientists to make better use of laboratory animal data (usually obtained at high-dose exposures) in estimating the effects of low-dose exposures in humans. Another major role of markers is clarification of the extent of exposure in human populations. Methods of direct or indirect measurement of total exposure through analysis of body fluids are far more likely to be of value in epidemiological studies than are most of the modeling and ambient monitoring approaches now in use. Biomarkers of exposure also hold the promise of demonstrating which individuals in a potentially affected population (e.g., residents in the neighborhood of a hazardous waste dump) have inordinate levels of exposure. Developments in the field of biological markers are also likely to lead to a more accurate determination of the proportion of highly susceptible people within the population (*30*) and of the results of human exposure.

Since health risk is determined by a complex of exposures and effects in humans, *in vivo* studies in a variety of laboratory-animal models may be necessary to provide the background data required for the identification of appropriate biological markers. It will also be necessary to find markers that distinguish environmentally induced health changes from the background of disease due to other causes. Since the toxicity of some chemicals is mediated either by activation or by detoxification biotransformation reactions, and since these processes differ across species, it is important to establish that a test animal has a metabolic pathway similar to that of humans.

A frequent source of uncertainty in risk assessment is the shape of the dose-response curve at low levels of exposure (*29,31*). It is often impractical to conduct animal studies of effects at low doses, mainly because large numbers of animals are required to detect the relatively low incidence of effects that result from such exposures. Furthermore, environmentally induced health effects in humans are usually associated with high exposures and hence high risk. Sensitive molecular markers being developed will permit study of the relationships between low ambient levels of chemicals and the formation of a predictive molecular marker. This could lead to the demonstration of dose-response relationships pertinent to low-level human exposure.

None of these benefits or other potential benefits of biological markers will be possible, however, without extensive and continued research on the basic mechanisms by which chemicals interact with tissues and organs of humans and other organisms. The need to further our understanding of the biochemical interactions involved in the development of disease remains the first priority for environmental health research.

Ethical Issues

A number of important ethical issues have been raised about the use of biological markers (*32–35*), especially about markers of susceptibility. Does society have an obligation to protect individuals beyond informing them of their risk? Can an employee be forced to leave his or her job once a susceptibility marker has been detected? There is concern that focusing on the detection of susceptible individuals could replace efforts to remove toxic chemicals from the workplace. Other ethical considerations arise from the degree to which susceptibility markers are predictive. For instance, it makes a difference whether the marker is totally predictive of an

adverse response, reasonably highly predictive, or only minimally predictive.

Ethical issues also extend to the use of markers for making decisions about consumer products. For example, should an item of value or of convenience to the general public be withdrawn from commerce because a few individuals are susceptible to adverse effects from use of the product, or should susceptible individuals be responsible for avoiding contact with the product?

The history of our civilization contains many examples of ethical issues and questions raised by new developments in science and technology. As we move rapidly into an era of greater understanding of the interactions between genetic material and exogenous chemicals or other important biological interactions, we must anticipate and be prepared to address the ethical issues that will certainly arise.

Proceedings of the Symposium

The papers that follow reflect the individual perspectives of their authors on current understanding of biological markers in four areas: male reproductive toxicology, female reproductive toxicology, toxicological exposures during pregnancy, and neurodevelopmental toxicology. In general, toxicological studies in these fields have not yet reached the hazard identification stage. Much research in these areas is still needed to understand the mechanism of the relationship between exposure and health effect. Biological markers can be used to gain insight into these mechanisms, as well as to describe the empirical associations between exposures and outcomes.

This introductory article is presented by the Committee on Biological Markers sponsored by the Board on Environmental Studies and Toxicology of the Commission on Life Sciences of the National Research Council. Further information about the study in progress may be obtained by addressing correspondence to the committee at the National Research Council, 2101 Constitution Avenue, N.W., Washington, DC 20418.

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