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Using Biomonitoring Data For Risk Characterization

Dr. Jo Anne Shatkin, The Cadmus Group, Inc.
Brent Ranalli, The Cadmus Group, Inc.

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Introduction

This report presents a brief introduction to biomonitoring, with an emphasis on the uses of human biomonitoring data for risk characterization and its applicability for drinking water. The report briefly summarizes the findings of recent workshops and panel reports on biomonitoring research needs, and it outlines current activities in this area conducted by the U.S. Environmental Protection Agency (EPA) and other agencies and organizations. It concludes with a discussion of possible future directions for biomonitoring efforts.

Background

What is Biomonitoring?

Biomonitoring is short for biological monitoring, or the monitoring of environmental contaminants in tissues and other biological media, such as urine, blood, and breast milk of organisms including humans. This report focuses primarily on human biomonitoring.

Biomonitoring measures biological markers (also known as biomarkers) of exposure to environmental contaminants. Biomarkers can include chemicals and their breakdown products produced in the body (metabolites), as well as DNA mutations or specific proteins associated with exposure to specific chemicals.

How Can Biomonitoring Data Be Used?

Traditionally, EPA and other agencies characterize risk to humans by extrapolating chemical doses applied in animal toxicological studies. The extrapolation relates the doses in test animals to estimated human doses, adjusting for body mass and accounting for physiological differences across species. Animal doses are typically adjusted for differences between species, as well as uncertainty in the actual effect levels and variability within species, by applying uncertainty and modifying factors. Biomonitoring promises to refine the traditional risk characterization procedure. It can provide a more nuanced understanding of the fate and behavior of chemicals inside animals of different species that validates, improves, or alters pharmacokinetic modeling and the relation of external exposure to target tissue dose.

In clinical and epidemiological applications, biomonitoring can help better characterize exposure directly in human subjects as well. Biomonitoring is used in occupational exposure assessment to measure employee exposure to workplace contaminants. In one recent high-profile case, the Centers for Disease Control and Prevention (CDC) used blood and urine samples to compare chemical exposures of firefighters who responded to the World Trade Center fires and collapse with firefighters in a control group (Edelman et al. 2003). EPA uses biomonitoring data as indicators for the potential for exposure to environmental contaminants. EPA conducted a survey of adipose tissue levels beginning in 1976, the National Human Adipose Tissue Survey, although this is no longer considered representative. Researchers are also considering seriological monitoring of antibodies as indicators of infection by specific waterborne pathogens (Casemore 2006).

National-scale biomonitoring data can measure and assess trends in environmental exposure to a variety of pollutants. Biomonitoring data can be used to enhance disease prevention efforts by assisting in defining the relationships between ambient pollutant concentrations, exposure to pollutants and health outcomes. Biomonitoring can also provide baseline data on "background concentrations" for identifying elevated exposures in sub-populations. It can be used in epidemiological studies and, if relationships can be defined, could change the basis of exposure assessment methods currently used.

Biomonitoring data offer the opportunity to improve assumptions EPA currently makes in estimating the relative source contribution (RSC) of drinking water to total exposure. EPA has used a default assumption of 20 percent RSC (i.e., an assumption that 20 percent of total dietary exposure comes from drinking water) as the lowest, most conservative estimate of the RSC. When a more precise RSC has been required, EPA has calculated one by evaluating all sources of exposure, in several cases (i.e., cadmium, chromium and selenium) using estimates of dietary intake of contaminants from the Food and Drug Administration's Total Diet Study. EPA has subtracted the dietary intake value from the Reference Dose (RfD) and then used the remainder as the allowance for water. Biomonitoring could provide a more direct estimate of contaminant exposures from drinking water and other media by correlating concentrations in those media with concentrations measured in tissue.

Rather than rely solely on studies in laboratory animals exposed to high levels of individual contaminants, as is now the case, future monitoring techniques relying on measures from emerging fields such as genomics and proteomics may be able to inform EPA and others about effects associated with cumulative exposure to drinking water contaminants.

Biomonitoring is also a tool for identifying emerging contaminants. For example, the discovery of perfluorinated compounds in wildlife and humans led to efforts to better assess sources of exposure to specific compounds and the risks they pose.

What Are the Challenges of Using Biomonitoring Data?

Exposure assessment is a key component of risk characterization, and biomonitoring data provide a direct measure of exposure to environmental contaminants. However, a number of complexities limit the ability of researchers to relate biomonitoring data to sources of exposure

for more than a handful of very well studied contaminants, such as lead and mercury. For emerging contaminants, biomonitoring data may be indicators of exposure, but not necessarily quantitative tools for risk assessment, until a better understanding of the relationships between environmental exposure, ingested dose, measured biological concentrations, and adverse health effects can be determined.

One difficulty is the need to correlate environmental concentrations of a contaminant to biological measures, because there may be many sources of exposure, including drinking water, food, air, and consumer/medical products. There is also a temporal aspect to exposure. That is, some contaminants may accumulate from birth, and others may have complex pathways of absorption, distribution, metabolism, and excretion in the body. Deciding which tissues to study, and which metabolites to measure, requires a detailed understanding of metabolic pathways, as described below in the summary of the 2004 International Life Sciences Institute workshop discussion later in this paper.

Biomonitoring data can be used to establish a baseline and evaluate trends in exposure. Population variability in measured levels can be assessed. The measurements will have uncertainty associated with them, and studies must be carefully designed so the data are interpretable. For example, when serum levels of a particular contaminant reflect a range of concentrations, it may be unclear how much of that variability relates to human metabolic variability and how much relates to variability in environmental exposure levels.

Sampling issues are complex and include determining which media are appropriate to sample. Urine sampling for contaminants such as pesticide metabolites is noninvasive, but requires adjustment for urinary excretion rates. This adjustment generally is made by normalizing contaminant concentrations on the basis of creatinine[1] levels in urine; however, creatinine levels vary with age, sex, race, and body mass index. In some cases, contaminants are rapidly metabolized, so their metabolites are measured. Metabolite levels may reflect more than direct contaminant exposure; they could also reflect exposure to degradates in the environment. For some contaminants, measuring blood levels may be a more direct measure; however, blood tests are invasive. Breast milk, saliva, hair, skin, and nails are other potential media, but their usefulness depends on the properties and behavior of the substance (Bradman and Whyatt 2005).

In a 2006 report (NRC 2006), the National Research Council (NRC) notes that while the volume of biomonitoring data has increased quickly in recent years, our ability to meaningfully interpret the data lags significantly. Some news media reports simply note that chemicals are present in human tissue, without providing any context about what levels reflect background and what levels are safe. Better alternatives include descriptive or risk-based approaches. A descriptive approach compares chemical concentrations in subject tissue to "normal" levels found in a reference population (for example, using percentiles). A risk-based approach attempts to determine whether the concentrations found in tissue pose a health risk using toxicology, epidemiology, or pharmacokinetic modeling data. Risk-based approaches are clearly preferable,

[1] Creatinine is a breakdown product of creatine in muscle tissue. Produced at a relatively constant rate, it is carried by blood to the kidneys and excreted in urine.

but we often lack the data needed to perform them, and they often involve modeling and extrapolations that introduce uncertainties into the analysis.

NRC recognizes three types of risk-based approach to evaluating biomonitoring data. The strongest is "biomonitoring-based risk assessment," in which biomonitoring data are correlated with epidemiological findings to establish biomarkers as indicators of specific public health risks (as has been done with lead and mercury). An alternative is the correlation of biomonitoring data and a human exposure assessment with toxicological findings from animal models (as has been done with glyphosate and permethrin). When epidemiological and exposure data are unavailable, a "biomonitoring-led risk assessment" can be conducted using pharmacokinetic modeling techniques to derive exposure values from tissue concentrations (as has been done with dioxin, chlorpyrifos, and phthalates).

Recent Reports on Research Needs

At least three different groups have convened in recent years to identify research needs, data gaps, and challenges faced by biomonitoring research programs.

International Life Sciences Institute (ILSI) Workshop, September 2004

The International Life Sciences Institute, in partnership with EPA, CDC, Agency for Toxic Substances and Disease Registry (ATSDR) and International Council of Chemical Associations (ICCA), sponsored a workshop on September 20 and 21, 2004, to address issues associated with the use of human biomonitoring data in exposure and risk assessment (Albertini et al. 2006). Considerations included understanding the environmental transport and fate pathways. For many emerging contaminants, behavior in the environment and the relationship to human exposure are poorly understood. Key issues in human exposure assessment identified at the workshop include understanding the primary sources and pathways of exposure, relating exposure to animal toxicology studies, gathering information about the exposure-to-dose relationship, and considering temporal aspects of exposure.

Dose-response data are needed to understand the differences between the animals and humans and to interpret measured tissue levels. Toxicology data are needed if biomonitoring data are to be used for risk assessment. The relationship between measured dose and effects must be determined. Background or reference data sets are needed to establish trends and identify elevated exposure levels. Biomonitoring studies require careful design; there is a need for guidance on this topic. The development of new technologies (e.g., gene expression, proteomics, and nano-sensor technology) will greatly expand biomonitoring capabilities, but a similar level of investment in complementary data will be required so interpretation to health risk can be made (Albertini et al. 2006).

One case study examined at the workshop, representative of the challenge of interpreting biomonitoring results, attempted to use biomonitoring to address risk assessment questions concerning polybrominated flame retardants (PBDE). The investigators concluded, "Significant gaps in our ability to interpret PBDE biomonitoring data to address public health and risk assessment questions include limited knowledge of environmental fate and transport of PBDE

congeners, limited population-based data for adults, and lack of data for potentially vulnerable populations such as children" (Birnbaum et al. 2006).

Research Foundation for Health and Environmental Effects (RFHEE) Workshop, November 2004

On November 13, 2004, the Research Foundation for Health and Environmental Effects (RFHEE) convened a workshop to discuss best practices and needs related to biomonitoring study design, interpretation, and communication (Bates et al. 2005). Specific study design issues discussed included the need:

- For ethical guidelines, because human studies can be controversial (guidelines established by Oleskey et al. 2004 for pesticide studies may be broadly applicable to biomonitoring studies).

- To address the challenge of adequate tissue banking.

- To ensure that chemicals are rationally prioritized for study (e.g., based on toxicity, ability to bioaccumulate, known exposure in sensitive populations, etc., not just the existence of analytical techniques).

- To ensure that sound statistical sampling techniques and laboratory analytical techniques are employed and that non-detects are properly reported.

- To ensure that the correct matrix (tissue or fluid) is chosen for sampling .

Specific interpretation issues included the following.

- Ideally, one would want biomonitoring to correlate exposure and effect, that is, the biological measurement could be related both to environmental exposure and to a specific health effect. These relationships are complex and require further investigation.

- Even with biomonitoring data in hand, interspecies comparisons need to be made with caution because differences between test animal and human pharmacokinetic parameters remain a source of uncertainty. Indeed, genetic differences can lead to inter-individual variability as well.

- Interpreting biomonitoring data is currently more appropriate for population-based risk assessments than clinical interpretation, but even this use requires improved population-based data collection, such as disease registries.

Specific communication issues included the need:

- For communication tools to provide study participants, the media, and the public with accurate information about the significance of biomonitoring data and how to interpret them.

X For a central location on the Internet where scientists can share and compare biomonitoring data and a robust public database of biomonitoring data and supporting information that have been collected.

National Research Council 2006 Report

In 2004, Congress directed EPA to ask the NRC to review current biomonitoring research practices, including the interpretation and communication of biomonitoring data. NRC released its findings 2 years later in the report *Human Biomonitoring for Environmental Chemicals*.

Across the board, NRC recommends improving the scientific database so higher quality risk assessments can be performed using biomonitoring data. NRC also recommends that future biomonitoring studies be paired with epidemiology, toxicology, and exposure investigations to enable better interpretation of the data.

Since interpreting biomonitoring results is far from simple, and data are collected directly from members of the public who have a personal interest in study findings, NRC also devotes special attention to communication issues. NRC outlines a conceptual framework for characterizing biomarkers and biomonitoring data in the report that it hopes will help facilitate communication among scientists, policy makers, and the public. NRC offers several practical suggestions including expanded biomonitoring education, communication training, and alerting the public about how to reduce exposure to chemicals of concern. NRC recommends that research-sponsoring agencies require in all funding applications plans for communicating results. NRC also encourages agencies to sponsor research specifically into risk perception and effective communication.

NRC makes additional recommendations about the design of biomonitoring studies. Specifically, NRC recommends that CDC, EPA, the National Institutes of Health (NIH), and other agencies develop a coordinated scientific strategy to identify analytes so that research efforts do not overlook contaminants of significant public health interest. NRC emphasizes the importance of using appropriate statistical principles in study design and taking cofactors into consideration. It recommends that analytical techniques and laboratory practices be further standardized and improved. NRC also urges that ethical issues raised by biomonitoring, including confidentiality, informed consent, reporting of results, and public health or clinical follow-up, be addressed.

What is EPA Doing Now?

EPA performs biomonitoring of aquatic organisms through Environmental Monitoring and Assessment Program (EMAP) and other programs, but these are not focused on drinking water.

EPA uses biomonitoring of lead and mercury to understand exposure and risk from drinking water and other sources. The Agency has developed multi-compartment pharmacokinetic and exposure models to relate multi-media environmental levels of lead to

blood lead levels in children (EPA 2004). EPA has related environmental exposures to lead and mercury to human exposure levels and health effects, so the biomonitoring data can be used in risk characterization and can be related to environmental concentrations in specific media.

What Are Others Doing?

There are several sets of nationally representative biomonitoring data. The CDC collects biomonitoring data every 2 years as part of the National Health and Nutrition Examination Survey (NHANES). In 2005, measurements were made for 155 chemical substances including pesticides and their degradates, heavy metals, phthalates, and aromatic hydrocarbons (PAHs, PCBs) (CDC 2005). Other data sets include the Agricultural Health Study, the Farm Family Exposure Study, and pilot studies as part of the National Human Exposure Assessment Survey (NHEXAS; Albertini et al. 2005).

European data sources include a German initiative, as well as European Union-funded biomonitoring data. The German Human Biomonitoring Commission was established in 1992 to derive scientifically sound criteria for using human biomonitoring data. The commission has collected large data sets, including data specifically on children. It has derived human biomonitoring (HBM) values (concentration thresholds associated with anticipated health effects) for lead, cadmium, mercury and pentachlorophenol in blood and urine, and has used representative sampling to establish population reference values for several metals, pesticides, phthalates, and polychlorinated biphenyls in blood, urine, and breast milk.

In September 2006, the State of California established the California Environmental Contaminants Biomonitoring Program. The program is to be managed by the California Department of Health Services in collaboration with the California Environmental Protection Agency. Biomonitoring will be conducted statewide by volunteers who are representative of the state's age, economic, racial, and ethnic composition. The CDC's *National Reports on Human Exposure to Environmental Chemicals* lists chemicals that are eligible for monitoring, plus additional chemicals that may be specified pursuant to state law. A nine-member Scientific Guidance Panel, expected to be named by September 1, 2007, will provide oversight. The program's first formal report is expected in 2010.

The National Ambient Water Quality Assessment (NAWQA) of the United States Geologic Survey (USGS) includes biomonitoring of aquatic organisms in representative watersheds.

Non-government organizations (e.g., Environmental Working Group, World Wildlife Fund) have collected some biomonitoring data, but these data are generally illustrative. They have not been collected in a statistical framework and are not representative of national exposure levels.

Potential Issues for the Future

The preceding discussion suggests that much work is needed for biomonitoring data to be useful in risk assessments for potential drinking water contaminants. A variety of issues could be addressed by EPA, other agencies, research organizations, academia, etc. In funding and designing biomonitoring studies, entities could:

- X Prioritize drinking water contaminants for biomonitoring investigation.

- X Establish guidelines for sound study design, in terms of statistical design, choice of appropriate biological media, sample handling, and analytical methods, as well as ethical considerations and communication with participants and the public.

- X Identify and prioritize areas of deficient data (e.g., background or reference data sets such as disease registries, understanding of the fate and metabolism of particular contaminants in the body, understanding of inter-species differences and intra-species variation).

- X Encourage or require those who collect biomonitoring data in the future to also collect route-of-exposure and human health effects data, and encourage those who conduct traditional exposure and health studies to incorporate biomarkers into their study design.

- X Improve and standardize laboratory techniques.

- X Develop advanced biomonitoring techniques such as gene expression, proteomics, and nano-sensor technology.

In communicating about biomonitoring data, organizations could:

- X Develop an online clearinghouse of human biomonitoring data for scientists.

- X Expand efforts to help the news media and the public understand what biomonitoring is and how to interpret biomonitoring results.

- X Fund research into public perception of biomonitoring and the risks associated with contaminant exposure, and into communication strategies.

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