

Workshop report

Understanding human biomonitoring

1. A workshop's report

The International Society of Regulatory Toxicology and Pharmacology hosted a workshop in Sacramento, CA, on 16 June 2005 to explore scientific and technical issues regarding human biomonitoring programs. The objective of the workshop was to identify areas of scientific agreement that may assist researchers, public health officials, regulators, and policy makers in developing and implementing biomonitoring efforts at local, regional, and national levels. Seven presentations addressed a range of issues including the scope of biomonitoring programs, study design, resource allocation, data collection, sample analysis, data analysis and interpretation, causality assessment, risk assessment, and communication. A panel discussion then identified general agreement regarding several aspects: (1) biomonitoring data may provide the most relevant information regarding human exposures if the data are carefully collected and interpreted; (2) even when properly conducted, biomonitoring results alone only address exposures, and cannot provide information regarding human health risks without complementary data from appropriate pharmacokinetic and pharmacodynamic studies; (3) the validity of biomonitoring data, and hence, the utility of biomonitoring programs requires strict adherence to scientific principles and quality assurance and quality control at all levels, from study design to interpretation and communication; and (4) interpretation and communication procedures need to be integrated and designed into a biomonitoring study from the beginning.

2. Background and summary of presentations

The United States Centers for Disease Control and Prevention (CDC) defines biomonitoring as "...the direct assessment of human exposure to environmental chemicals by measuring the chemicals or their breakdown products (metabolites) in people's blood or urine." The CDC has conducted biomonitoring for environmental chemicals as part of its National Health

and Nutrition Examination Survey (NHANES) since the late 1990s, and currently releases the results of these efforts in its National Report on Human Exposure to Environmental Chemicals (<http://www.cdc.gov/exposurereport/3rd>). It is hoped that biomonitoring will not only identify human exposures to environmental chemicals, but will also provide a basis for understanding potential associations between exposure and disease in the human population.

Despite the fact that human biomonitoring programs have been ongoing for many years, a number of scientific and technical issues related to these programs are still in need of resolution and further development. In particular, advancements in analytical chemistry have enabled the detection of many chemicals in human samples at levels less than one part per billion, and for some chemicals, at levels below one part per trillion. Although these advancements permit researchers to more accurately quantify human exposures to environmental chemicals and to do so with greater certainty and less variability than ever before, biomonitoring does not answer a number of important questions. As employed in most studies, biomonitoring indicates substances present in the body at a single point in time, corresponding to when the specimen was taken, but such data alone provide no information on the source, the magnitude, the frequency or the duration of exposure, and the CDC has been careful to note that "[T]he measurement of an environmental chemical in a person's blood or urine does not by itself mean that the chemical causes disease." Thus, as human biomonitoring studies and programs advance and continue to be implemented by local, national, and international laboratories, challenges and opportunities are increasingly posed across the public and private sectors to understand and interpret study results. To address these challenges and opportunities, the workshop's morning session focused on the scope of biomonitoring programs and their study design; the afternoon session focused on the challenges biomonitoring presents for the laboratory, for risk assessors and health professionals, for understanding environmental causation, and for professionals engaged in communicating results to the public.

2.1. Morning session of the workshop: the scope of biomonitoring programs

Dr. David Galbraith (ChemRisk) explained how biomonitoring data provides information on the amount of a chemical that is absorbed and retained in the body from a variety of exposure sources, and thus reduces reliance on assumptions implicit in models that predict internal chemical levels from exposure data. Biomonitoring serves as a biomarker of exposure, but may or may not help to identify the source or level of exposure, depending on requisite ancillary data. Various human tissues and fluids (e.g., blood/serum, urine, fat, hair, breast milk, saliva/sputum, and semen) can be used to test chemical levels, but each type of medium must be evaluated carefully because physical and biological characteristics can affect the utility for measuring specific chemicals. The advantages and limitations of the particular biological medium used must be considered in the interpretation of biomonitoring data for specific chemicals.

Galbraith emphasized how improper interpretation and communication of biomonitoring data can lead to unnecessary public alarm. In California and elsewhere, publicity surrounding the mere presence of persistent organic pollutants in human milk led to concern about risks to nursing infants. Reporting this information without the proper context generated public fear, which compelled many respected health bodies (EPA, WHO, FDA, etc.) to reiterate that the well-documented benefits of breast feeding far outweigh any theoretical risks from contaminants and that breast milk remains the best nutritional source for infants. Galbraith opined that the current version of California Senate Bill 600 seeking to establish a statewide biomonitoring program lacks important components needed to relate biomonitoring data to public health, creating the potential to raise undue alarm. Galbraith stressed that both interpretation of biomonitoring results and thoughtful, science-based communications should be integral components of a biomonitoring program.

Dr. Larry Needham from the Centers for Disease Control and Prevention outlined the procedure for collecting biomonitoring data under the National Health and Nutrition Examination Survey (NHANES). He explained that the biomonitoring component of NHANES is an ongoing effort, spanning 2-year increments, each consisting of analysis of blood and urine for a specific set of chemicals. The objectives of CDC's biomonitoring program are to assess the exposure of the American population and subpopulations to specific substances, establish reference ranges, and track trends over time. The sampled population is a stratified, complex, multistage, probability sample of non-institutionalized civilians, and includes over-sampling for specific subpopulations. Results are communicated in the National

Reports on Human Exposure to Environmental Chemicals as geometric means and percentiles stratified for age, sex, and race.

Needham used lead, DDT/DDE, and dioxins as specific examples to illustrate the utility of human biomonitoring data, noting that methods to detect perfluorinated substances would be validated in the near future. Needham used data from banked specimens collected as part of the clinical and epidemiological investigations of the aftermath of the explosion of a trichlorophenol facility in Seveso, Italy in 1976 to illustrate how biomonitoring data are useful for aggregating and confirming exposure groups. CDC's analysis revealed that TCDD levels were highest in individuals who developed chloracne and resided in the zone most heavily exposed. The data also revealed variance in susceptibility, with chloracne developing in some, but not all individuals who had high serum levels of TCDD. A follow-up epidemiological investigation found a skewed sex ratio for children born to parents in the highest exposure zone up to 1984, and parents with the very highest TCDD levels begat only female children. The sex ratio of newborns returned to normal between 1985 and 1994. This type of information is possible only because specimens had been banked and biomonitoring was able to accurately measure individual blood levels.

Dr. Judith LaKind (LaKind Associates) summarized the recommendations of an expert panel on biomonitoring convened by the Research Foundation for Health and Environmental Effects (RFHEE) in 2004 to evaluate issues related to study design, data interpretation, and communication (Environmental Health Perspectives, online July 6 at <http://dx.doi.org>). The Panel concluded that all the elements of human biomonitoring—study design, scientifically justified interpretive procedures, and communications tailored to specific audiences—are required for a study to be both scientifically sound and to make a significant contribution to public health.

LaKind reported that the Panel's recommendations regarding study design included procedures for chemical selection, chain of custody, specimen integrity, quality assurance, and quality control. She noted that not only must institutional human study review committees approve study designs, but investigators should also consider outreach efforts to address interests of the public and stakeholders. The Panel recommended considerable attention be paid to developing a science-based process to interpret biomonitoring results, and emphasized the need to understand the audience(s) that will receive information from biomonitoring programs in order to determine the best means for developing informative materials and for communicating key messages. Scientific manuscripts are necessary but insufficient to fully communicate to concerned audiences. Investigators should recognize that because biomonitoring data may be readily misinterpreted, they must clearly differentiate

between statistically significant changes and clinically significant effects. Currently, there is no established architecture for reporting, communicating and collating population-based and individual-based biomonitoring data. Even though challenges exist, adoption of a common architecture would facilitate cross study comparisons and advance research efforts to better understand what health impacts, if any, are associated with specific levels of biomonitored substances.

In a lunchtime address, Dr. Richard Jackson shared his experiences at the CDC and California's state public health agency, stressing the epidemiologic power of human biomonitoring and its potential to improve public health decision-making. Jackson concluded that biomonitoring projects at state or regional levels are inevitable, but to be effective, must be designed and conducted correctly, modeled on standards set by CDC's NHANES and National Exposure Reports. Jackson supported biomonitoring in California, but noted that it must be "done right," and that educational efforts should both precede and parallel biomonitoring reports in order for the data to be understood and used effectively by public health and environmental protection agencies, policy and decision makers, and public stakeholders.

2.2. Afternoon session of the workshop: the challenges of biomonitoring

Dr. Jeffrey Wong (Department of Toxic Substances Control, California EPA) addressed the challenges faced by biomonitoring laboratories. He drew upon his experience directing the DTSC Hazardous Materials Lab, which has had success in developing protocols for measuring various substances in diverse media/specimens, and stressed that collaboration with other labs is the key to solving methodological problems. Analysis of biological specimens for low, environmentally relevant levels of substances requires trained and dedicated professional staff, expensive and delicate laboratory instrumentation, and a firm commitment to implementing and adhering to quality assurance and quality control procedures. Furthermore, operating a biomonitoring laboratory requires the financial means to purchase supplies, equipment and standards, maintain and upgrade instrumentation, and recruit, train, and retain qualified professional staff. Wong noted that these are ongoing and significant challenges that can impact the ability of a laboratory to conduct a sufficient quantity of reliable and reproducible data to support large-scale biomonitoring programs.

Dr. Christopher Borgert (Applied Pharmacology & Toxicology) focused on philosophical and statistical issues of causality assessment linking exposure and disease. He used causality criteria developed by Henle-Koch and Hill to differentiate between linear, deterministic causalism and more complex causal constellations

or mosaics. Borgert explained that while strictly linear causalism rarely occurs, approaches based on the causal constellation/mosaic theory become practically useless because they render it nearly impossible to refute or objectively confirm any specific causal proposition. He argued that to address causality, a comprehensive science-based process is needed in which the entirety of the scientific evidence is evaluated in a rigorous, unbiased manner.

Borgert's presentation explained why biomonitoring alone cannot address causality, and that overlaying biomonitoring results with disease incidence rates for a given population or locale is insufficient to assign cause and effect. Borgert reasoned that in public health and legal areas, there is an obligation to determine whether sufficient data exists to make a scientific determination about cause. He provided a series of questions to address when considering the role of biomonitoring data in a scientific assessment of causality, including: the unequivocal identification of the disease; confirmation that diseased individuals are more exposed than non-diseased; accuracy and statistical variance of chemical measurements; relationship of internal chemical levels to external exposure and dose; identification, elimination or control of all other potential causal factors in the analysis; repeatability; and biological relevance of the results (temporal and mechanistic coherence of cause-effect hypotheses—e.g., biological plausibility).

Sean Hays (Summit Toxicology) contrasted the rapid advancements in ability to detect low levels of chemicals with the slow pace of advancing knowledge about relationships between internal dose and health risks. Even though the complex human exposure situation cannot be determined from a single biological measurement, such interpretations are made frequently and increase the uncertainty in health risk estimates based on biomonitoring data. Hays noted that for most substances other than pharmaceuticals, toxicity, dose response, and pharmacokinetic information from humans is unavailable and must be extrapolated from animal studies to interpret biomonitoring data.

As a surrogate for detailed human data, Hays explained that risk assessors must rely on physiologically based pharmacokinetic (PBPK) models and more limited human data to predict internal doses based on external exposures. In many cases, these models can help interpret human biomonitoring levels by predicting the internal dose (and population variation) associated with external contact to a specified exposure level, and can also be used to "back calculate" the applied dose that corresponds to biomonitoring measurements; estimated applied doses can be compared to the NOAEL or LOAEL to derive a margin-of-exposure. The validity of such exercises, however, is dependent on the scientific integrity of both the biomonitoring data and the

exposure assumptions. When rigorously validated, these methods can assist the interpretation of biomonitoring data in a health risk context, often with greater certainty than conventional, scenario-based, default-driven risk assessments, as well as provide a means to verify the effectiveness of risk management strategies.

Dr. Robert Krieger (University of California, Riverside) addressed the challenges faced in communicating biomonitoring data to the public and policy makers. Krieger explained that a fundamental public misunderstanding is that any degree of exposure to a so-called “toxic substance” implies harm, which underscores the importance of education and outreach efforts that emphasize dose response as a critical determinant of potential risk. Krieger explained that the ACGIH TLVs and BEIs are examples where health criteria have been developed and utilized to benchmark against exposure and biomonitoring levels to gauge, manage, and communicate potential health threats. He argued that development of an index for biomonitoring data, applicable to the public at large, similar to an ACGIH BEI, is greatly needed and is within the realm of possibility with collaborations between analytical laboratories, health professionals, and regulatory agencies.

Krieger cautioned health professionals, however, that gaining acceptance of the principle that “small amounts may be of no health consequence” will be challenging and admonished that this critical principle is essential in biomonitoring communications. He stressed that education and outreach should explain that chemical exposures are an ever-present characteristic of daily life, recognizing that the strong emotional reaction to biomonitoring information is likely to require extra effort by health professionals to infuse science into the biomonitoring communications and policy arenas.

3. Roundtable discussion

All speakers participated in a roundtable discussion that was open to meeting participants. The overarching conclusions and recommendations of this session included:

- Study designs should follow ethical standards, be rigorously developed, and approved by interdisciplinary professionals to assure that protocols for sample

collection, analysis, interpretation, and communication are scientifically rigorous and transparent to stakeholders.

- Laboratory methods must be validated and appropriate QA/QC procedures must be fully implemented.
- The ability to detect and quantify substances in human specimens is currently much greater than the ability to fully interpret the data toxicologically. This underscores the need to focus on education and outreach efforts that convey biomonitoring data credibly, within appropriate limits.
- Biomonitoring studies have emerged as important and useful components of comprehensive environmental public health programs, for quantifying age, gender and race specific exposures in populations, in establishing population specific reference ranges of background levels, and in tracking trends over time.
- Biomonitoring alone cannot distinguish differential contributions from various sources such as natural, anthropogenic, workplace, consumer products, foods, and normal biologic processes.
- Biomonitoring has an important, but limited role in establishing causality. Overlaying biomonitoring data with locale or population disease incidence does not form a scientific foundation for causal conclusions.
- Biomonitoring has the potential to become the “gold standard” for exposure assessment. However, to interpret biomonitoring results in a health risk context, a new paradigm is needed that provides guidance on “safe” biomarker levels, perhaps employing PBPK modeling in combination with “no-effect” or minimal risk toxicity benchmarks.

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