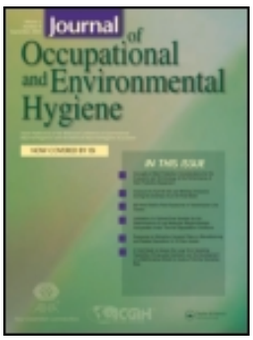

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A Summary of the Workshop "Applying Biomarkers to Occupational Health Practice"

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INTRODUCTION

In 1996 the National Institute for Occupational Safety and Health (NIOSH) engaged more than 500 organizations and individuals representing labor, industry, government, and academia, in a process to identify occupational safety and health research priorities for the United States. This process identified 21 priority research areas that became the National Occupational Research Agenda (NORA). One of these priority areas is exposure assessment methods. Methods may be defined as "tools, approaches, and strategies that are used in, or enable, the conduct of exposure assessments in the workplace." In order to explore the issues related to occupational exposure assessment, a team—the *NORA Exposure Assessment Methods Team*, comprised of researchers and public health professionals from industry, labor, academia, and government—was formed. To completely understand how biomarkers and research could be augmented, strengthened, developed, and applied to key exposure assessment issues, the *NORA Exposure Assessment Methods Team* sponsored a workshop entitled "Applying Biomarkers to Occupational Health Practice" in Santa Fe, N.M., on March 24–25, 2003. Cosponsors of the workshop included the American Industrial Hygiene Association, Society of Toxicology, and National Medical Services, Inc.

The workshop was designed to bring together individuals studying worker populations, researchers developing and validating new biomarkers, and occupational health practitioners in order to foster future collaborations and identify research gaps and priorities in the application of biomarkers to occupational health practice. Since air concentrations of occupational toxicants represent only potential exposures and many workplace exposures occur through the dermal route, a primary workshop goal was to improve the understanding of biomarkers and promote their effective application in estimating exposure to occupational hazards. Biomarkers can help determine actual exposures and subsequent effects of those exposures. A second goal was to discuss prevention of occupational illness by utilizing biomarkers of exposure or early effects to determine the need to eliminate or minimize exposure. The workshop targeted multidisciplinary occupational health professionals including: biologists, chemists, toxicologists, industrial hygienists, and epidemiologists. While the first day focused on plenary presentations concerning biomarker development, application, and ethical, legal, and social issues, the second day followed a more traditional workshop model.

APPLYING BIOMARKERS—THE TOXICOLOGY PERSPECTIVE

Dr. Claude Viau (University of Montreal, Montreal, Canada) discussed principles of toxicology and how biomarkers might be selected using those principles. Hydroxypyrene, a biomarker for polycyclic aromatic hydrocarbons, was used to

illustrate the application of toxicology principles for biomarker selection. Dr. Viau noted that the choice of a biomarker is based on several types of toxicologic information including in vitro studies, animal in vivo/in vitro studies, human volunteer studies, and field studies. He acknowledged the importance of toxicokinetics as a key concept in biomarker development and stressed that researchers should know the absorption, distribution, biotransformation, and excretion of a compound. He discussed the influence of exposure to mixtures on biomarker concentrations. Dr. Viau closed by adding that biological monitoring is useful in orienting preventive measures only when reference values are available for the selected biomarkers. These reference values can be derived from the distribution of biomarker concentrations observed in reference (or nonexposed) populations, from the relationship between toxicity endpoints and biomarker concentrations, and/or from the relationship between biomarker concentrations and airborne exposure concentration.

DEVELOPMENT OF BIOMARKERS

Dr. John Groopman (Johns Hopkins University, Baltimore, Md.) talked about the processes associated with the development and validation of biomarkers using the carcinogen aflatoxin as an example. He explained how population-based studies have been used to attempt to understand high-risk populations in an occupational setting. However, he cautioned that since people are exposed to a variety of carcinogens, their overall health pattern must be investigated. He added that biomarkers are not only useful to evaluate exposure, but also have application to monitor risk. Dr. Groopman argued that chemical specific markers tend to underestimate the risk and that there is not a one-to-one correlation between exposure and dose. He closed by noting that biomarkers must be validated in the laboratory and for the exposure/disease being investigated.

USE OF BIOMARKERS

The role of the Biological Exposures Indices (BEI) of the American Conference of Governmental Industrial Hygienists and issues on the practical use of biomarkers were described by Dr. Michael Morgan (University of Washington, Seattle, Wash.). He discussed practical issues of biomarker use: the need for reference values, whether guidelines or standards are available, what are important indicators of exposure, the validity of the biomarker, and what confounders or interferences might be present. Other issues he acknowledged included the need for toxicology data to aid in the interpretation of the marker, the desirability of a marker that indicates a reversible condition, and the costs associated with biomarker analysis. Dr. Morgan noted that biological exposure indices are one of several classes of reference values that may not correlate to airborne concentrations and that certain criteria are considered before a BEI is developed: whether the chemical has a systemic distribution, how many people are exposed, the demand for the chemical, and whether sufficient toxicokinetic and human data exist for the chemical.

BIOMARKER RESEARCH FOR RISK ASSESSMENT

Dr. Michael Jayjock (Rohm and Haas, Spring House, Pa.) introduced the principles of hormesis for risk assessment. Dr. Jayjock defined hormesis as an overall positive or stimulatory effect seen at low doses that appears to provide beneficial effects. There is little human data at low doses and most data used for risk assessment is orders of magnitude removed from concentrations at which people are normally exposed. He emphasized that biomarker research needs to focus on markers of effects at realistic environmental concentrations.

ETHICAL, LEGAL, AND SOCIAL ISSUES

Dr. Paul Schulte (NIOSH) presented a summary of ethical, legal, and social issues related to human subjects research. Dr. Schulte emphasized that participant rights are paramount in conducting human studies. These include the rights of autonomy, respect, beneficence, nonmalficence, privacy, and confidentiality. He explained that the informed consent document enlightens participants about why the study is being done, how the study is going to be conducted, and how participants will be notified of their results. It also informs the participant of any social, legal, and economic consequences and may describe potential follow-up work. Dr. Schulte discussed the problem of reductionism that can occur with population-based studies. Reductionism is when a health effect or disease is attributed to only one exposure or specific gene. He noted that human health problems are complex and can be caused by a number of factors and other determinants. Researchers must be cautioned not to overstate their results.

WORKSHOP

On the second day, three breakout groups were formed to discuss research needs and gaps in the following areas: (1) development of new biomarkers, (2) application of biomarkers in research and exposure assessment, and (3) use of biomarkers in risk assessment/management. The breakout groups were chaired by Drs. Regina Santella (Columbia University, New York, N.Y.), Melissa McDiarmid (University of Maryland, College Park, Md.), and Robert Tardiff (The Sapphire Group, Washington, D.C.), respectively. Before the breakout groups began their deliberations, an overview of the problem for discussion was presented by each of the chairs. Dr. Santella described the research she has conducted in developing biomarkers for polycyclic aromatic hydrocarbons. Dr. McDiarmid discussed her work on the use of biomarkers to evaluate kidney damage, and Dr. Tardiff presented a description of the risk management process.

At the conclusion of the three stimulating and enthusiastic breakout sessions, the meeting reconvened as a plenary session where summaries of each breakout groups' deliberations were presented. Several common central themes emerged: development of new biomarkers, validation of new and existing biomarkers, prioritization of biomarker development and agent to be studied, development of guidelines, initiation of partnerships, and re-evaluation of existing documents and risk assessments using biomarker data. Each is discussed briefly below.

Development of New Biomarkers

In general, there is an ongoing need for new biomarker development. New methods and application of state-of-the-art technology are desirable and necessary. Since many biomarkers rely on blood or other tissues as surrogates, development of noninvasive techniques or methods are particularly attractive. In addition to the development of new biomarkers, investigation of workplace exposures may benefit if multiple biomarkers or a panel of biomarkers were used in the assessment.

Validation of New and Existing Biomarkers

Validation of biomarkers is imperative. Very few reference values or standards are currently available. Biomarker analysis should be conducted in quality control/quality assurance programs that include proficiency testing. The development of criteria for validation would be useful.

Prioritization of Biomarker Development and Agents to be Studied

Prioritization of biomarker development and agents to be studied would ensure that limited resources are used wisely. A prioritization scheme that others can follow easily should be created.

Development of Guidelines

Various types of guidelines or handbooks would be most useful. A manual discussing available biomarkers, suggestions for workplace application of these biomarkers, and communicating results to workers would be worthwhile. Furthermore, a biological monitoring manual may be a useful tool to standardize methods.

Initiation of Partnerships

In order for biomarkers to be used more frequently and successfully in occupational health practice, the establishment of partnerships for biomarker development, validation, and communication was deemed important. Multidisciplinary teams should be created that include toxicologists, chemists, industrial hygienists, medical personnel, epidemiologists, and risk assessors, so that study results would have widespread use within the occupational health community. Specimen banking should be considered so that human samples are available as new biomarkers are developed.

Re-Evaluation of Existing Documents and Risk Assessments Using Biomarker Data

It was further suggested that published documents, such as criteria documents or risk assessments should be re-evaluated and rewritten (if applicable) to include information garnered from biomarker research.

The workshop concluded with two presentations on how biomarkers are currently being used by regulatory agencies in Germany and the United States.

THE GERMAN APPROACH

Substituting for Dr. Hans Drexler (University of Erlangen-Nuremberg, Erlangen, Germany), Dr. Glenn Talaska (University of Cincinnati, Cincinnati, Ohio) discussed the German approach to biological monitoring, which is centered on occupational health physicians. In this system, the Deutsche Forschungsgemeinschaft (German Research Foundation), for the setting of threshold limit values at the workplace, and the Berufsgenossenschaften (Statutory accident prevention and insurance institutions), for the implementation of biological monitoring at the workplace, play an essential role. The benefits are that experts are supported to provide guidelines and to develop the biomonitoring program, a quality control program is established including round-robins for biomarkers, and the physicians have the authorization to conduct biological monitoring.

THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION (OSHA) APPROACH

Ms. Caroline Freeman (OSHA, Washington, D.C.) used cadmium as an example of how her agency has utilized biological monitoring. In the development of a biological monitoring standard at OSHA, issues such as material health impairment, significant risk, benefits, and costs of a federal standard must be addressed. In addition to good research data, laboratory standardization, medical surveillance protocols, determination of methods and how the methods were chosen, the burden on the employers and employees, cost, and invasive or noninvasive nature of the technique are also considered. She emphasized that despite good, clear-cut research data, it took 6 years to develop the cadmium standard. Ms. Freeman concluded that for OSHA to include biomonitoring in their standards, more well-designed human studies evaluating biomarkers is an absolute necessity.

CONCLUSIONS

Biomonitoring has been used in the research setting for a long time to investigate exposure and effects of ex-

posure, but the transition to occupational health practice has lagged for many reasons. Validation of a biomarker is a key for its use in practice. Practitioners need to be able to interpret the meaning of a biomarker. Biomonitoring data is sometimes more difficult to interpret because of inter- and intra-individual variability. In addition, practitioners need interpretative information to notify workers of the meaning of their results. However, as these issues are resolved, biomonitoring should become a mainstay in occupational health practice.