

# Emerging Issues

in Environmental Health Sciences

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The Newsletter of the  
Committee on Emerging Issues and  
Data on Environmental Contaminants

## Focused Efforts in Toxicogenomics

“We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time.” Dr. Bennett Van Houten, Science Advisor to the NIEHS Toxicogenomics Research Consortium, opened the second meeting of the Committee on Emerging Issues and Data on Environmental Contaminants with this quote from T. S. Eliot. The meeting, held at the National Academies on February 6, 2003, addressed a spectrum of efforts taking place in the field of toxicogenomics, including the development of public databases, the standardization of data collection from microarray experiments, the optimization of knowledge management, and the integration of toxicogenomics data into risk assessment.

Dr. Van Houten provided an overview of the efforts taking place at the NIEHS National Center for Toxicogenomics (NCT). One major effort is the NCT’s toxicogenomic database, referred to as Chemical Effects in Biological Systems (CEBS). CEBS will integrate microarray data and gene expression images with general toxicology and pathology data, allowing for a comprehensive approach to relating environmental exposures to biological responses. In a second effort, the NCT’s Toxicogenomic Research Consortium (TRC) is seeking to standardize toxicogenomic experiments on gene expression and examining molecular responses to environmental stressors. Gene expression profiling will help elucidate the answers to questions such as: Which genes are activated or suppressed by environmental stressors? Is there conservation of responses across species and

pathways? Do environmental contaminants have unique signatures of exposure or toxicity? Are there differences in gene responses to acute and chronic exposures? And what gene expression changes lead to injury or disease? The TRC is supporting research in trans-species comparisons, cross platform comparisons, dose and time effects, cell cycle regulation, metabolism of xenobiotics, and working to create standards and tools for bioinformatics. Dr. Van Houten concluded his talk by posing the important question, “Can these data be repeated by different laboratories, using different platforms?”

Dr. Brenda Weis, Extramural Toxicogenomic Research Coordinator at NIEHS, addressed this important question by discussing the approach the TRC is using to standardize gene expression profiling data. She explained that at present there are no standard protocols. Individual centers have

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# Potential Challenges to Use of Toxicogenomics Noted by Federal Agencies

The Federal Liaison Group (FLG) to the Committee on Emerging Issues and Data on Environmental Contaminants consists of representatives of a variety of governmental agencies interested in toxicogenomics. The FLG met at the National Institutes of Health on February 5, 2003 to outline key areas that might pose potential challenges to the implementation of new toxicogenomics technologies by the federal government. These challenges were then presented to the National Academies' Committee on Emerging Issues and Data on Environmental Contaminants

at an open meeting of the Committee on February 6, 2003.

Four potential challenges to the use of toxicogenomics microarray data in governmental agencies were identified by the FLG: premature use of data; data interpretation per se; communications; and information gaps.

One challenge is the potential premature use of microarray data. Regulatory agencies and the regulated industries need criteria to judge when a technology should be considered mature enough to be used for regulatory purposes. To this end, stages

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## *Agencies of the Federal Liaison Group*

**Occupational Safety and Health Administration**

**U.S. Environmental Protection Agency**

**U.S. Department of Energy**

**Department of Defense**

**National Institute for Occupational Safety and Health**

**U.S. Department of Agriculture**

**Food and Drug Administration**

**Centers for Disease Control and Prevention**

**Agency for Toxic Substances and Disease Registry**

**U.S. Patent and Trademark Office**

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*This newsletter as well as additional information about the committee and its activities can be found at <http://dels.nas.edu/emergingissues>.*

*The newsletter of the Committee on Emerging Issues and Data on Environmental Contaminants, "Emerging Issues in Environmental Health Sciences," is published to keep you informed of committee activities. This is a joint project of the National Research Council's Board on Environmental Studies and Toxicology and Board on Life Sciences.*

# Public Willingness to Participate in Genomics Research

Mark A. Rothstein, J.D.  
University of Louisville School of Medicine

Public opinion often has a major impact on public policy development, particularly in areas such as biomedical research, where breakthroughs are announced before the public has a chance to be educated about their implications. Policies involving toxicogenomics are likely to depend on the public's understanding of, and views about, the new research and its perceived effect on their lives. Similarly, the public's view of the research might impact its willingness to participate in basic research and take advantage of medical advancements dependent on genetic information. Although there have not been any comprehensive national surveys of public attitudes toward toxicogenomics, a recent study of public attitudes toward pharmacogenomic research sheds light on toxicogenomic research issues. Two issues explored in a recent survey, willingness to participate in research and trust in different types of organizations, are discussed here as they are particularly relevant to genomic research in general.

The recent survey was the first detailed

nationwide telephone interview survey on pharmacogenomics. Approximately 1,800 individuals were interviewed, using oversampling to achieve a minimum subgroup size of 300 for whites, African Americans, Hispanics, and Asians.

The willingness of individuals to participate in genetic research was explored by asking individuals

if they would be willing to participate in research under the following four conditions: (1) if it was anonymous, (2) if medical records were used in addition to biological samples, (3) if research findings would be shared with other researchers, and (4) if there was a possibility of developing a treatment. A large majority (80%) said they were very likely (46%) or somewhat likely (34%) to participate if their participation meant the possibility of



developing a treatment. This was in line with expectations, but anonymity was far less of a factor in favorable responses than expected. In fact, overall, the number likely to participate under conditions of anonymity was similar to those who would participate if medical records were linked with samples and if information was shared with other researchers.

The relative importance of anonymity varied by age. Those in the 30-39 age category were most likely to view anonymity as important; those over the age of 60 were the least likely to view anonymity as important. It was theorized that the younger group was more concerned about possible adverse economic consequences stemming from disclosure of genetic information than was the older group, which was more likely to be approaching or at retirement age and more likely to be moving from private health insurance to Medicare.

*Mark Rothstein is a member of the Committee on Emerging Issues and Data on Environmental Contaminants. He is the Chair of Law and Medicine and Director of the Institute for Bioethics, Health Policy and Law at the University of Louisville. The complete pharmacogenomics study may be found in Rothstein, MA and C.A. Hornung. 2003. Public attitudes about pharmacogenomics. In Pharmacogenomics: Social, Ethical, and Clinical Dimensions, M.A. Rothstein, ed. Hoboken, NJ: John Wiley and Sons.*

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# Public Willingness

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In many instances, researchers trade off the value of individually identifiable information to develop a protocol that they think will be more acceptable to potential research subjects. Based on this survey, researchers may be able to more confidently design research protocols without anonymity, so long as other safeguards are in place to protect confidentiality.

The public's trust in different types of institutions was explored by assessing willingness to participate in research conducted by: (1) universities and medical schools, (2) the federal government, (3) pharmaceutical companies, and (4) health organizations, like the American Cancer Society and March of Dimes. The responses varied widely by institution and demographic factors. In general, trust levels for universities and medical schools and health organizations were comparably high. Trust levels for the federal government and drug companies were comparably low. Trust levels for universities and medical schools increased with respondent age, but the other institutions stayed about the same across all age groups. Hispanics and Asians had the highest levels of trust in the federal government; whites and African Americans had the lowest levels of trust in the federal government. For African Americans, trust in the federal government decreases sharply with education, which the authors speculate is a function of the knowledge of the Tuskegee syphilis study.

What can be taken from these data about trust in different research entities is that some institutions may need to work harder to overcome distrust. It is also apparent that it is essential to design, conduct, and report research in a culturally sensitive manner. Researchers would be wise to recognize the suspicion with which medical research is viewed by some racial/ethnic groups. Accordingly, researchers will be received more positively if they involve the community in the study's planning, recruitment, and dissemination stages.

In summary, empirical research about public attitudes is valuable to decision makers in

identifying areas of public concern and valuable to researchers as genomics research is likely to advance less contentiously when public viewpoints are taken into consideration. The data generated in this pharmacogenomics survey suggest several areas of possible follow-up for research involving toxicogenomics. ●

## Focused Efforts

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very good data, but it is almost impossible to compare data from different laboratories. Specifically, there are three layers of variation that exist within a microarray experiment: biological (treatment, cell or animal model, animal husbandry), technical (tissue and RNA extraction), and array format and design (chip design, labeling/hybridization, scanning, statistical analysis). Dr. Weis outlined how the TRC is addressing the technical aspects of variation through collaborative standardization experiments performed by NCT and extramural research centers to improve the reliability, reproducibility, and quality of toxicogenomic data.

Ms. Cyril Pettit of the International Life Science, described similar efforts underway to address technical variations associated with microarray experimentation, develop a public database that is compliant with the minimum-information-about-a-microarray-experiment (MIAME) criteria, and investigate whether known mechanisms and pathways of toxicity could be associated with characteristic gene expression profiles. She interpreted the data collected thus far as an indicator of gene expression patterns consistent with known biology; however, she pointed out that gene-by-gene comparisons and the level of variation across laboratories pose significant barriers to using toxicogenomic data in risk assessment.

The presentation by Dr. Chris Stoeckert, Penn Center for Bioinformatics, University of Pennsylvania, centered on the need for microarray standards at the level of bioinformatics. He

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## Focused Efforts

Continued from previous page explained that MIAME and Microarray Gene Expression (MAGE) data exchange formats were being created to standardize the content and structure of information from any given experiment so that it could be entered properly into a database to allow the data from different researchers to be shared and compared. Dr. Stoecker forecast the future of toxicogenomic databases and predicted that entering microarray data into a database using (MIAME/MAGE) would someday be similar to entering DNA and protein sequences into the National Center for Biotechnology Information database.

Dr. Donna Mendrick of Gene Logic Inc., one of several biotechnology firms currently

employing these gene expression technologies, concluded the panel presentations by explaining some of the toxicogenomic endeavors her company was pursuing. She described efforts underway to use gene expression profiling to develop organ-specific predictive models of chemical-induced toxicity. She asserted that both the company's in vitro and/or in vivo models were sensitive enough to distinguish between genetic signatures produced as a result of general toxic responses and those produced by specific classes of toxins (e.g. hepatotoxins). Dr. Mendrick emphasized that these models had great potential for improving our ability to predict whether or not an unknown chemical is toxic and highlighted their benefits for both drug development and environmental health. ●

## The Metabonome: An Integral Part of the Systems Toxicology Paradigm

Timothy Zacharewski, Ph.D. Michigan State University

*Tim Zacharewski is a member of the Committee on Emerging Issues and Data on Environmental Contaminants. He is Associate Professor in the Department of Biochemistry and Molecular Biology at Michigan State University.*

Many pharmaceutical, consumer product, and chemical companies, as well as regulatory agencies, are currently evaluating the utility of genomic and proteomic technologies to assess product safety and identify cellular responses to environmental contaminants. To fully assess the potential adverse effects of exposure to drugs, chemicals, and natural products, an integrated systematic understanding of the molecular, cellular, and physiological effects is required within the context of the whole organism. However, cellular activity is not dictated by gene and protein expression alone. Gene and protein expression and

their associated biochemical networks can also be dramatically affected by metabolites. Recent meetings (e.g., California Separation Science Society's Systemics (November 3-6, 2002); NIEHS' Metabolic Profiling: Application to Toxicology and Risk Reduction (May 14, 2003)) have highlighted the importance of metabonomics.

Metabonomics is defined as the quantitative measurement of multiparametric metabolic responses of multi-cellular systems to pathophysiological stimuli or genetic modification. It is an *in vivo* systematic approach that uses nuclear magnetic resonance (NMR) or mass spectrometry (MS) to assess changes in metabolite levels within biological fluids (e.g., urine, plasma, cerebrospinal) and tissues. It nicely complements genomics and proteomics, and has the additional advantages of being quantitative, sensitive, and non-invasive. Metabonomic techniques also permit high throughput, simple sample preparation, sample preservation, and the ability to collect multiple samples from the same experimental unit over time. Despite the volume

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# Potential Challenges

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in the evolution of toxicogenomic science should be characterized to provide a framework for determining where different technologies are in the continuum from basic research to applied technology.

A second challenge was characterized as the danger of flawed interpretations of data by the scientific community. The limitations of microarray data and a range of definitions for validation of the methods and techniques should be described. It was suggested that the scientific community needed a mechanism to determine when a scientific consensus was being approached or had already been reached.

Educating stakeholders on the new science is a third challenge. Clear and accurate communication within and outside the scientific community, however, will depend on appropriately describing the benefits, limitations, and timelines for using toxicogenomics technologies. One critical issue that will need to be addressed is the role of toxicogenomics in legal matters and fair access to and use of toxicogenomics information by all parties.

A fourth challenge is information gaps. One question is whether the “the right experiments will get done” to address the most critical information gaps. It may be most appropriate for experiments that will help the evolution of the field to be completed first, particularly those that focus on proof of concept. Cross species comparisons may be one difficult area that can be focused on soon. There is also a need for risk assessment-oriented evaluations that link structure-activity relationships (SAR) and source identification to human health outcomes using these new technologies. Addressing other challenges could help fill information gaps. Specifically, cross-platform and laboratory harmonization and the development of common standards for data generation and reporting will enhance the ability to integrate information.

As the science of toxicogenomics advances, the needs of the government agencies using this technology will also change. In particular, there are needs for mechanisms to share data between

agencies and researchers, to coordinate reference sets and database development, and to establish links between the various toxicology databases, especially those in the private sector. Further dialog between regulators and scientists on concepts, such as a “safe harbor,” may also advance the use of information in regulation. There is also a growing need for identification and description of success stories for specific applications that validate the use of toxicogenomics technologies and that explain the appropriate use of “systems biology” approaches to toxicogenomics.

With many of the FLG agencies engaged in risk assessment, the integration of toxicogenomics into this field is critical. Some of the issues that will need to be considered are the use of SAR, dealing with mixtures, moving from the chemical-by-chemical paradigm to grouping of chemicals with similar actions, identifying sensitive subpopulations, and ethical concerns such as the monitoring of susceptibilities in workers. The federal agencies are closely watching this burgeoning field in the hopes that it will provide valuable information to help them protect human health and the environment. ●

## The Metabonome

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of data amassed individually, the true power of genomics, proteomics and metabonomics lies in the integration of these technologies and in the incorporation of complementary traditional toxicology data. Metabonomics helps close the loop on “omic” technologies by measuring functional outcomes that accompany changes in gene expression and protein levels. It is important to consider the “omic” technologies together to take advantage of the synergies that exist between them. Consequently, a future challenge will be the identification of metabolite changes that signal potential adverse effects, the integration of these data with the data generated by genomic and proteomic technologies, and ultimately the use of this combined information in an integrated approach to decision making. ●

## Morning (8:00 AM - 12:30 PM)

### Introduction to Information-Gathering Session

David Eaton, Committee Chair and John Quackenbush, Session Chair

### Issues in experimental design and data representation

*What are the challenges in designing and describing experiments? Are current techniques sufficient?*

Kathleen Kerr, University of Washington  
Susanna-Assunta Sansone, European Bioinformatics Institute

Discussion led by committee members Tim Zacharewski & Thomas Skopek

### Controlled vocabularies and XML-based data exchange

*What is the state of the art? Are the existing standards sufficient?*

Catherine Ball, Stanford University  
Paul Spellman, Lawrence Berkeley National Laboratory

Discussion led by committee members Bing Ren & Cheryl Walker

### Challenges in creating expression databases

*What information needs to be stored? How should multiple site data be integrated? Is MIAME sufficient to capture data relevant to toxicological studies?*

Roger Bumgarner, University of Washington

Discussion led by committee members Jim Bus & Linda Greer

**For more information, please contact Jennifer Saunders by phone at 202-334-2616, or by e-mail at [jsaunders@nas.edu](mailto:jsaunders@nas.edu).**

## Afternoon (1:30 PM - 6:00 PM)

### Issues in data analysis

*How are significant genes in functional genomics data found? What is important for sample classification and prognostic prediction?*

Sandrine Dudoit, University of California-Berkeley

Discussion led by committee members Casimir Kulikowski & Ken Ramos

### Challenges in fields other than microarrays

*How do proteomics and metabonomics complement functional genomics? Do we know enough about the proteome or metabolic pathways to make sense of the data?*

Pedro Mendes, Virginia Bioinformatics Institute

Richard Smith, Pacific Northwest Research Laboratory

Discussion led by committee member John Quackenbush

### Roundtable Discussion of Committee Members, Sponsoring Agencies, and Workshop Participants

Roundtable chaired by John Quackenbush & David Eaton

# QUESTIONS ABOUT THE APPLICATION OF “-OMICS” APPROACHES TO TOXICOLOGY: An Information Gathering Session

TUESDAY, SEPTEMBER 16, 2003

Held at:

The University of Washington Campus  
4225 N. Roosevelt Way, NE, Room 229  
Seattle, Washington

Sponsored by the Committee on Emerging Issues and Data on Environmental Contaminants to inform discussion of challenges in bioinformation that may be addressed by future projects. Session speakers will discuss some of the fundamental issues that need to be resolved in order to apply microarray approaches and other new technologies to toxicological challenges.

Committee on Emerging Issues and Data on Environmental Contaminants  
Board on Environmental Studies and Toxicology  
Board on Life Sciences  
THE NATIONAL ACADEMIES  
500 Fifth Street NW  
Washington, DC 20001



## **An Invitation to** **Questions and Issues in the Applica-** **tion of “-Omics” to Toxicology**

TUESDAY, SEPTEMBER 16, 2003

Held at:  
The University of Washington  
4225 N. Roosevelt Way, NE, Room 229  
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