



# Emerging Issues

in Environmental Health Sciences

Issue 2  
January 2003

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

## Symposium on Toxicogenomics Launches New National Academies Program

“What puts people at risk? Can toxicogenomics help us understand the biology behind what makes us sick and what doesn’t?” These questions from Richard Harris of National Public Radio set the stage for the first meeting of the National Academies’ newly established Committee on Emerging Issues and Data on Environmental Contaminants. The symposium, held at the National Academies Building on November 4 and 5, 2002, addressed the “new biology” revolution in environmental health sciences, and covered a broad spectrum of topics on how new technologies such as genomics, and toxicogenomics in particular, may improve public health by improving toxicology. And like most revolutions, this one has engaged a variety of players, ranging from lab bench toxicologists and geneticists to lawyers and insurance companies.

Dr. Kenneth Olden, director of the National Institute of Environmental Health Sciences, had asked the National Academies to establish the Committee on Emerging Issues to provide a public forum to examine the impact that the new technologies will have on the practices of toxicology, bioinformatics, risk assessment, and public health. In his introduction to the symposium, he emphasized that the environment to which people are exposed includes more than chemicals and drugs; it also comprises physical surroundings, nutrition, lifestyle, and biological, social, and economic factors.

The committee was encouraged by National Center for Toxicogenomics Director Dr. Ray Tennant to consider issues such as how the new technologies can be harmonized, how adverse effects should be defined based on microarray data, how the volumes of data should be acquired and managed, and how to define the components of a toxicogenomics knowledge base.

Beware of “genetic exceptionalism,” a major barrier to making genomics useful in the public health arena, cautioned Dr. Gil Omenn of the University of Michigan. He noted that it is important to link genetic variation with socioeconomic factors that also influence a

person’s health. Early and ongoing community involvement is also critical to helping the public understand the benefits and limitations of toxicogenomics.

Public education was also the focus of Barbara Culliton’s talk. Editor-in-chief of Genome News Network, Culliton emphasized that there are already misperceptions on the part of the public that range from “we are being poisoned and don’t know it” to “you are scaring us needlessly.” Scientists will have to work hard to provide sound information about what these technologies will mean to the public.

The legal implications of toxicogenomics for both litigation and environmental regulation were discussed by Dr. Gary Marchant of Arizona State University. Gene expression data and individual susceptibility, due to genetic differences, are two aspects of genomic data with which the courts are grappling.

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# Symposium Launches New Program

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David Craford of Affymetrix, one of the biotechnology firms developing these new technologies, described some of the new gene expression tools that are used in genomics, proteomics, and metabonomics. He demonstrated how microarrays have been automated and commercialized, resulting in a vastly increased number of genes that can be analyzed at the same time, reducing the time and costs involved in making and using the gene chips. Management of these volumes of genomic data was the focus of the presentation by Dr. William Mattes of Pharmacia.

Computer databases and computerized analyses are the only ways to capture, maintain, search, and extract the data. Dr. Carol Henry of the American Chemistry Council addressed the implications of these technolo-

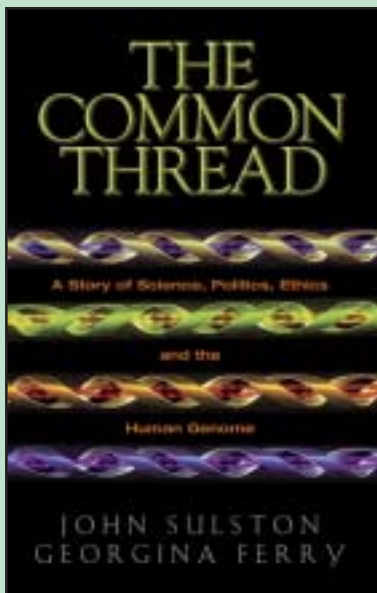
gies for the practice of risk assessment. Although there is great promise in the application of genomics to toxicology, this science is still in its infancy, and at present there are more questions than answers.

The symposium concluded with short presentations by members of a federal liaison group organized to assist the committee. The group, convened by the NIEHS, consists of representatives of federal agencies with an interest in toxicogenomics, such as the Food and Drug Administration, the U.S. Environmental Protection Agency, and the Department of Energy (see the article on the federal liaison group on page 6 for more details). Common themes among the agencies were the need for a unified research agenda and effective public communication. ●

## *A call for ethical responsibility in research*

In *The Common Thread*, John Sulston takes us behind the scenes for an in-depth look at the controversial sequencing of the Human Genome. *The Common Thread* is a compelling history and an impassioned call for ethical responsibility in scientific research. John Sulston was director of the Sanger Centre in Cambridge, England, where he led the British arm of the international team selected to work on the Human Genome Project. He was knighted in the 2001 New Year's Honours List for his contribution to science and is the winner of the 2002 Nobel Prize for Physiology or Medicine.

Available from the National Academies Press online, at <http://www.nap.edu/catalog/10373.html>.



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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 symposium news. This is a joint project of the National Research Council's Board on Environmental Studies and Toxicology and Board on Life Sciences.*

# Emerging Issues in Toxicogenomics

Toxicologists and other environmental health scientists face challenges in taking advantage of the rapid advances in toxicogenomics. Mindful of this, the National Academies' Committee on Emerging Issues and Data on Environmental Contaminants is developing ideas to be explored in studies and at future meetings. The committee's role is to identify and outline important questions that should be addressed by the National Academies, the NIEHS, and others. (See Hot Topics for more information on this page.)

At the next meeting, the committee will discuss several of these topics in open session to develop questions that could be addressed in focused studies. Specifically, the committee will consider the following: (1) how knowledge management can best be developed to take advantage of the new technological approaches, (2) the appropriate roles of the new technologies in risk assessment, and (3) how toxicological research should be influenced by the new technologies.

Knowledge management challenges facing researchers include storing toxicogenomic and proteomic data, designing query tools to use the data, coordinating data across individual laboratories, and dealing with proprietary data. Although the databases are growing rapidly, human genome data may be most useful when the methods are mature enough to be validated against traditional toxicological approaches. Some scientists anticipate that toxicogenomics will be useful under some circumstances, but that at present the science cannot be applied generally to traditional toxicological questions. Toxicogenomic data needs to be discussed in terms of what information the regulatory agencies can use, such as which gene expression

changes should be considered indicative of adverse effects, how the information might influence carcinogen assessment, how the information might help determine the use of default values, and how changes in gene or protein expression should be integrated over the life of the animal.

In parallel to committee efforts to identify important toxicogenomic issues, the NIEHS is engaged in several of the topics outlined above. For

example, the NIEHS is working on the assessment and validation of animal models and in December held a workshop on transgenic animal models and how they compare with standard laboratory animals in terms of live animal and tissue imaging. The National Toxicology Program also continues to collect tissue samples for future use in toxicogenomics, although the NIEHS realizes limita-

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## ***HOT TOPICS***

Topics that the committee might consider over the next several years include the following:

- How will the new technologies affect risk assessment? Should the 1983 NRC report *Risk Assessment in the Federal Government: Managing the Process*, the so-called "Red Book," be updated to address the new technologies and their potential impact on risk assessment? Will doing so require a major paradigm shift?
- How can we effectively communicate with the public about the advantages and limitations of toxicogenomics?
- How should new animal models be assessed and validated?
- How should toxicological tissue banks be developed and maintained? What can be done now to ensure future access to useful biological samples? What factors limit their use?
- How can advances in pharmacogenomics be applied to toxicogenomics?
- How can bioinformatics tools be developed, applied, and managed to produce the most helpful information?
- What are the privacy issues surrounding toxicogenomics, including possible misuses?
- How should toxicology graduate students and others be trained in the "new biology"?
- What are the promises of a "systems biology" approach in toxicology and risk assessment?
- What are the impacts of toxicogenomics advances on toxicological research?
- How should the environment be defined from the perspective of gene-environment interactions?

# NIEHS Coordinates Multiple Projects in New Toxicogenomics Field

Recent biological research and rapid advances in global genomic technologies have enabled scientists to better comprehend the molecular basis for life. Data produced by these new technologies have grown at unprecedented rates, but the analytical tools needed to understand and organize are only slowly being developed. Recognizing the need to support research, develop new technologies, and establish methods to use the burgeoning genomic, proteomic, and toxicogenomic data, the National Institute of Environmental Health Sciences (NIEHS) has actively supported intra- and extramural research programs through the efforts of the Environmental Genome Project (EGP), the National Center for Toxicogenomics (NCT), and the National Academies' Committee on Emerging Issues and Data on Environmental Contaminants.

NIEHS established the EGP in 1998 to "improve the understanding of human genetic susceptibility to environmental exposures." Two main activities supported under EGP include the Comparative Mouse Genomics Centers Consortium and human DNA polymorphism discovery and characterization research. The Comparative Mouse Genomics Centers Consortium comprises a number of academic centers using mouse models to understand the functional significance of human DNA polymorphism. The human DNA polymorphism discovery and characterization research focuses on the "resequencing and functional analysis of polymorphic variants in environmentally responsive genes."

Established in 2000 by NIEHS,

the mission of the NCT is to "coordinate a nationwide research effort for the development of a toxicogenomics knowledge base." The five goals of the NCT are facilitating the application of gene and protein expression technology; understanding the relationship between environmental exposures and human disease susceptibility; identifying useful biomarkers of disease and exposure to toxic substances; improving the computational methods for understanding the biological consequences of exposure and responses to exposure; and creating a public database of environmental effects of toxic substances in biological systems. The Chemical Effects in Biological Systems (CEBS) knowledge base will contain data on global gene expression, protein expression, me-

tabolite profiles, and associated chemical/stressor induced effects in multiple species (e.g., from yeast to humans).

NCT has both intramural (NIEHS Microarray Center, NCT Toxicology/Pathology Team, NIEHS Proteomics Program, and NIEHS intramural laboratories) and extramural components (Toxicogenomics Research Consortium (TRC), Division of Extramural Research and Training (DERT), TRC Working Group, and the Proteomics program). One of the major research components of NCT is the TRC, which serves as a primary extramural program for applying microarray technology. The TRC was established in 2001 when the NIEHS Di-

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## POTENTIAL FUTURE STUDIES

After discussions with the NIEHS and other participants at the open session, three proposals for new studies are being developed by the National Academies. These draft proposals will be reviewed at the next committee meeting, scheduled for February 6-7, 2003. The proposed studies are

- The potential impacts and limitations of emerging technologies on risk assessment and environmental decision-making
- Impact of new technologies on toxicology research
- Knowledge management for the new biology/technology

# NIEHS Coordinates Projects

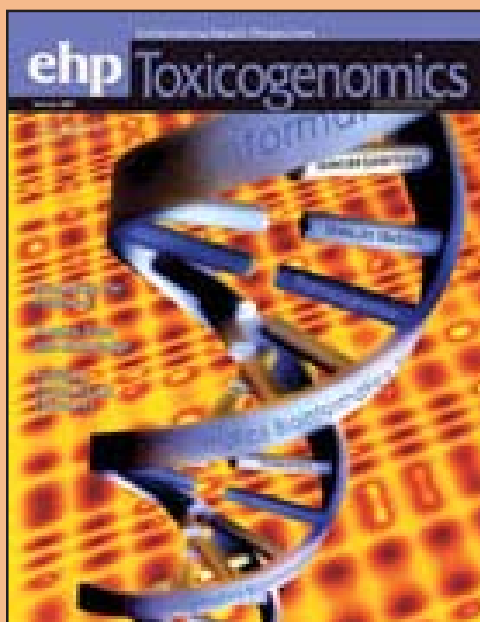
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vision of Extramural Research and Training (DERT) awarded grants to five institutions to participate in the TRC as cooperative research members. These five institutions (University of North Carolina at Chapel Hill; Fred Hutchinson Cancer Research Center, Seattle, Washington; Oregon Health Science University, Portland; Duke University, Durham, North Carolina; and Massachusetts Institute of Technology, Cambridge) and the NCT Microarray Group form the core of the consortium.

An important goal of the TRC is to “conduct a series of cooperative gene expression experiments using shared and complementary microarray platforms within the cooperative research members.” These experiments will be used to develop a number of important standards for conducting gene expression experiments, including standards for predicting high quality, reproducible data as well as technology standards and bioinformatics tools for data comparison.

Through programs such as the EGP, the NCT, and the National Academies’ Committee on Emerging Issues and Data on Environmental Contaminants, the NIEHS hopes to encourage research that explores the complexities of normal genetic and metabolic pathways. The results of this research should help biologists better understand the implications of pathway malfunction on disease occurrence and toxic response. ●

## Journal Focuses on New Field



The NIEHS has expanded its coverage of toxicogenomics with a new quarterly edition of the journal *Environmental Health Perspectives* entitled *EHP Toxicogenomics*.

Areas covered include pharmacogenomics,

proteomics, metabonomics, molecular epidemiology, translational aspects of genomic research, and molecular medicine. Dr. Kenneth Ramos, a member of the National Academies’ committee, is the editor of *EHP Toxicogenomics*. *EHP Toxicogenomics* can be found at <http://ehp.niehs.nih.gov/txg/>. Image credit: Michael Scott/EHP (from website).

## Emerging Issues in Toxicogenomics

*Continued from page 5*

tions may exist in the use of previously collected samples for toxicogenomics studies. NIEHS is also interested in efforts to train new researchers in toxicogenomics.

In conclusion, the NIEHS continues to work in many of the areas identified by the committee as important. The committee is currently working with the NIEHS and the federal liaison group members to identify and develop questions that

may require focused, in-depth studies to evaluate the best approaches and policies for taking advantage of the new information available to scientists. Additional questions may become evident at a workshop the committee anticipates organizing on “systems biology” and its relationship to risk assessment, to address the potential impact of a systems biology approach. ●

# Federal Liaison Group's Perspectives

The National Academies' Committee on Emerging Issues and Data on Environmental Contaminants will consider issues and opportunities that will affect a number of federal agencies. The committee members do not include current employees of NIEHS, the sponsoring institution, or other government agencies. Therefore, to provide a mechanism for the committee to learn more about challenges the new technologies create for federal agencies, the National Academies asked the NIEHS to organize a federal liaison group (FLG) with members from federal institutions that have interests in toxicology and risk assessment.

Most committee meetings will include time for discussions between the FLG members and the commit-

tee in sessions that are open to the public. The FLG will provide insights about how the different agencies are using data produced by the new technologies and the challenges the agencies face in applying this information, especially in regulatory situations. The FLG will also interact with the committee by providing feedback about topics and speakers for future workshops and other activities.

Federal agencies will face many promises and challenges in using the new technologies. Genomics, proteomics, and other new approaches will help them improve risk assessment within the agencies. Specifically, the new technologies might help them better assess the impact of individual genetic variability on

susceptibility and better understand the relevance of activation of different biological pathways in animals. Toxicogenomics maybe useful in determining early indicators of exposure. Challenges include the need for consensus on when and how new approaches should be validated and what constitutes a valid toxicity signature for a chemical. Practical issues include developing knowledge bases and mechanisms for submitting new types of data to regulatory agencies. Taking advantage of the new technologies will also require training both within and outside the agency. Public communication will be critical for the effective use of this new information.

Current federal liaison group members include:

**Steven Bayard, Ph.D.**

Director, Office of Risk Assessment  
Occupational Safety and Health Administration

**John Doll, Ph.D.**

Director  
United States Patent and Trademark Office  
Technology Centers

**William Farland, Ph.D.**

Acting Deputy Assistant Administrator for Science  
U.S. Environmental Protection Agency

**Marvin Frazier, Ph.D.**

Director, Health Effects and Life Sciences Research  
Division  
Office of Biological and Environmental Research  
U.S. Department of Energy

**Kevin Geiss, Ph.D.**

Senior Scientist  
Department of Defense

**Carol Maczka, Ph.D.**

Acting Director of Risk Assessment  
Food Safety and Inspection Service  
U.S. Department of Agriculture

**Albert E. Munson, Ph.D.**

Director, Health Effects  
National Institute for Occupational Safety and Health

**Lawrence Reiter, Ph.D.**

Director  
National Health and Environment Effects Research  
Laboratory  
U.S. Environmental Protection Agency

**Paul Schulte, Ph.D.**

Director, Education and Information Division  
National Institute for Occupational Safety and Health

**Bernard Schwetz, Ph.D.**

Acting Deputy Commissioner/Senior Advisor for  
Science  
Food and Drug Administration

**Tom Sinks, Ph.D.**

Associate Director for Science  
National Center for Environmental Health  
Centers for Disease Control and Prevention

**Frank Sistare, Ph.D.**

Director Scientist  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

**Robert Spengler, Ph.D.**

Associate Administrator for Science  
Agency for Toxic Substance and Disease Registry

**Hal Zenick, Ph.D.**

Associate Director for Health  
National Health and Environment Effects Research  
Laboratory  
U.S. Environmental Protection Agency ●

# GENERATING USEFUL INFORMATION

## IN TOXICOGENOMICS:

# FOCUSED EFFORTS

Please join us for the second meeting of  
the National Academies' Committee on  
Emerging Issues and Data on  
Environmental Contaminants

Room 100  
The National Academies  
500 Fifth Street, NW  
Washington, DC 20001

### THURSDAY, FEBRUARY 6, 2003

#### MORNING (9:00 AM - 12:30 PM)

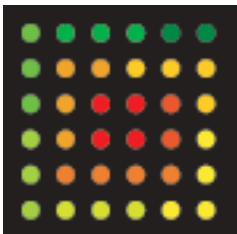
- 9:00 Welcome  
*David Eaton, Chair*
- 9:10 NIEHS Toxicology Research Consortium—Global aspects  
*Bennett Van Houten, NIEHS*
- 9:40 NIEHS Toxicology Research Consortium—Standardization experiments  
and other activities  
*Brenda Weis, NIEHS*
- 10:10 MIAME: Minimum Information About a Microarray Experiment  
*Chris Stoeckert, Penn Center for Bioinformatics,  
University of Pennsylvania*
- 10:40 Break
- 11:00 The International Life Sciences Institute efforts in toxicogenomics  
*Sybil Pettit, The International Life Sciences Institute (ILSI)*
- 11:30 Toxicogenomics efforts at Gene Logic  
*Donna Mendrick, Gene Logic Inc.*
- 12:00 Panel discussion

#### AFTERNOON (1:00 PM - 4:30 PM)

- 1:00 Report from Federal Liaison Group  
*Samuel H. Wilson, NIEHS*
- 1:30 Discussion of proposed projects
- ♦Potential impacts/limitations of emerging technologies  
on risk assessment and environmental decision-making
  - ♦Impact of new technologies on toxicology research
  - ♦Knowledge management for the new biology/technology
- 3:00 Break
- 3:15 Discussion of topics for future workshops/symposia
- 4:30 Adjourn

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

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 Generating Useful Information in Toxicogenomics: Focused Efforts**

THURSDAY, FEBRUARY 6, 2003

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Washington, DC 20001

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