

## Toxicogenomics and Risk Assessment

Risk assessment estimates the likelihood that exposure to a chemical will harm people by identifying the chemical's toxic effects, the doses at which those effects might occur, and whether a person might be exposed to those doses. Many environmental decisions are based on chemical risk assessments. Toxicogenomics is the intersection of toxicology and the new technologies that can be used to identify changes in gene expression and other biological processes. Regulatory agencies, such as EPA and FDA, are looking to toxicogenomic technologies to improve risk assessment of environmental contaminants and drugs, but the specifics of how to incorporate them into the regulatory process is less clear. Conversely, scientists working with these technologies, but unfamiliar with environmental or regulatory risk assessment, may not appreciate how their efforts might influence the risk assessment process or what role their data may play in filling knowledge gaps about how chemicals exert their toxic effects.

To try to bridge this gap in understanding, a one day workshop titled "How Toxicogenomics Technologies Could Inform Critical Issues in Carcinogenic Risk Assessment of Environmental Chemicals," was held on December 15<sup>th</sup>, 2003 at the request of the National Academies Committee on Emerging Issues and Data on Environmental Contaminants. Participants included scientists with expertise in "-omics" technologies, toxicology, risk assessment, epidemiology, public health, and risk communication. The workshop began with an overview of how data describing chemical effects can inform risk assessment and the challenges that are

typical of many risk assessments. It then shifted to a description of the types of toxicogenomics studies that might be relevant to risk assessment. Finally, two chemical risk assessments were used as case studies to illustrate real-world knowledge gaps and foster discussion of how these gaps might have been addressed with toxicogenomics information.

James Bus began the workshop by discussing how non-tumor data are used to improve in risk assessment. Non-tumor data are important because they can help us understand the underlying processes by which a chemical might cause cancer. These studies focus on whether a chemical causes changes in key biological processes such as absorption, distribution and metabolism in the body; possible mutations in a cell's DNA; and abnormal cell growth or death. Bus emphasized that such non-tumor data can help

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# FDA Releases Pharmacogenomic Guidance

By John Leighton Ph.D. and Karol Thompson Ph.D., Center for Drug Evaluation and Research,  
Food and Drug Administration

Although the field of pharmacogenomics is in the development stage, there is great potential for this technology to increase drug safety and efficacy through individualization of drug therapies and earlier identification of drug toxicities. This has led the FDA to issue a draft guidance on pharmacogenomics with the intent of encouraging the use of this technology in drug development. Especially within the field of toxicogenomics, there are many issues that remain to be resolved within the scientific community, such as data consistency, statistical methods validation, and the interpretation of the toxicological, pharmacological, and physiological significance of gene expression changes. Workshops that FDA held with the regulated industry in May 2002 and November 2003 explored the sciences of pharmacogenomics and pharmacogenetics in the

hope that such interactions could be incorporated and clinical. Out of these workshops

and other internal and external interactions, details were developed into a draft guidance document titled "Guidance for Industry: Pharmacogenomic Data Submissions." The guidance was written to be consistent with current regulations and practice but recognized the need for new approaches such as new informatic tools to address data submissions from global surveys of cellular physiology. The 90-day comment period has concluded, and it is now undergoing revision.

While maintaining consistency with current FDA regulations specifying regulatory submission requirements for Investigational New Drug Applications (IND), New Drug Applications (NDA), and Biologics License Applications (BLA), the guidance proposes a design for when pharmacogenomic data submission is required or voluntary, and whether full reports or summarized data are necessary. The

intent of the voluntary genomic data submissions (VGDS) proposal is to encourage use of this developing technology through a mechanism that informs both industry and regulators. This technology is thought to have much promise for smarter drug development, but only if it is put into use by the regulated industry and is adopted in an appropriate manner by regulators. This latter point is critical because while such studies are considered important for drug development, at this time they should be considered

only preliminary until issues surrounding analytical and biological validation are addressed. Thus, it is considered important that these studies be put in context with other toxicological data that are used to make safety decisions until the genomic data are considered of sufficient maturity to be used as "stand alone" study

data. Until these issues are addressed, it is important that the lead pharmaceutical compounds be analyzed

using all appropriate techniques so that the best possible decisions on which compounds to select for clinical development are made without imposing additional regulatory burdens.

In order to prepare a regulatory framework for and internal expertise in reviewing genomic data, a nonclinical pharmacogenomics subcommittee was formed in 2002 at CDER (FDA Center for Drug Evaluation and Research). The subcommittee is composed of CDER research scientists with laboratory experience in genomics and reviewers from most CDER drug review divisions, who have research backgrounds in molecular biology or genomics. There is also representation from CBER (FDA Center for Biologics Evaluation and Research) to provide the perspective of the biologics review divisions and to develop a consistent message across FDA. The subcommittee

**The draft document "Guidance for Industry: Pharmacogenomic Data Submission" is available on the FDA website at <http://www.fda.gov/cder/guidance/5900dft.pdf>.**

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determine low-dose effects, illustrate differences in responses by different animal species and genders, distinguish susceptible populations such as infants and the elderly, and identify biomarkers of a chemical's effects or exposure. He provided several examples of these types of studies. Aniline metabolites, formed in the liver, may damage circulating red blood cells. These damaged cells are then scavenged by the spleen and may cause abnormal cell functions, resulting in spleen tumors. If exposure to aniline is low enough to prevent damage to the red blood cells, spleen tumors may not occur. A second example is propylene glycol monoethyl ether that may cause tumors in rats via a protein that is not made in humans. It has been suggested that this chemical may not be a human carcinogen even though it causes cancer in rats.

After Bus explained the usefulness of non-tumor data for risk assessment, John Moore outlined common knowledge gaps that present challenges in cancer risk assessment. He began by explaining why epidemiological studies of humans are often insufficient for risk assessment. Information such as frequency and intensity of exposure may be lacking, making it difficult or impossible to establish a quantitative relationship between chemical exposures and human disease. Thus, animal studies are necessary despite the inherent uncertainties. Moore mentioned that there is also variability in response between different animal species—that a rat may develop

different cancers when exposed to a chemical than a mouse or monkey would. Other challenges include how to account for the variability in human population, including age, sex, and health status differences.

Workshop chair Linda Greer identified some additional knowledge gaps. She mentioned that information about how a chemical acts in the body is not always available. Furthermore, there may be a lack of information on whether males and females respond to chemicals differently and how responses to a given chemical may be different if it is mixed with other chemicals, including tobacco smoke, and the fact that people are exposed to a multitude of chemicals in their lifetimes. She also pointed out that variability in response of different tissues is another challenge.

Shifting from risk assessment approaches and uncertainties to the genomics technologies, Cheryl Walker discussed scientific challenges in using genomics data for cancer assessments by focusing on gene expression (microarray) data and its nature. Gene expression information is relatively qualitative data so it may be more useful for understanding the *potential* of a chemical to have an adverse effect rather than quantitating the effect of a *particular dose*. Walker distinguished two fundamental ways gene expression data may apply to toxicology: pattern recognition and insight into how a chemical affects biological processes. Walker explained that some patterns of gene expression changes might eventually be considered predictive of a toxic response and therefore useful in predictive toxicology, if they are reproducible and have an acceptable degree of correlation. Scientists may also need to determine how to reconcile different types of “-omics” information into a clear picture. For example, they may need to determine how to evaluate protein or metabolite data that appear to suggest different effects indicated by gene expression data.

Ken Ramos continued Dr. Walker's discussion on the utility of gene expression experiments. He noted that some research is focused on cataloging gene expression patterns that result from different chemical exposures. He also described how genomics data and may be useful in distinguishing different types of patients or different types of tumors. Ramos then described an approach to learning more about how chemicals exert their effects. Scientists typically look

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**For more information on risk assessment, access the EPA Risk Assessment Forum <http://cfpub1.epa.gov/ncea/raf>.**

**The Risk Assessment Forum is a standing committee of senior EPA scientists which was established to promote Agency-wide consensus on difficult and controversial risk assessment issues and to ensure that this consensus is incorporated into appropriate Agency risk assessment guidance.**


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at the decrease or increase in the expression of hundreds of genes in response to a chemical exposure and try to interpret what these changes reveal about what is happening to the cells. One approach is to use modeling to systematically analyze a variety of different genes, to see which genes may interact with each other in response to a chemical exposure. By understanding which genes interact, new biological understanding might emerge. That is, while a decrease or increase in expression of a few genes might not appear to cause substantial changes in a cell, a group of genes that interact together in a particular network might actually be predictive of specific biological effects. Elucidating networks and identifying which genes interact with others can help scientists better understand biological processes that result in cancer.

The workshop then shifted to discussing two “case studies.” David Eaton and Ken Ramos reviewed butadiene and arsenic risk assessments. They then opened up the discussion to how toxicogenomics information might have helped resolve some of the issues that arose when these chemicals’ carcinogenicity was just beginning to be studied. The workshop audience discussed ideas such as using genomics to determine multiple ways that a single chemical can act, and using genomics to understand the biological basis of discordant results between human and animal data or between different animal species. Another proposal

was to see if a chemical affects different tissues in distinct ways. It was also suggested that the range of susceptibility among different humans and the relationship to differences in human genetic makeup be studied. Others thought that genomics could help in understanding different diseases and subtypes of disease, e.g., not only cancer in general but specific types of cancers. Human epidemiology data were also mentioned, with the idea that genomics markers might help with exposure characterization. One audience member asked if genomics information might be useful if combined with information on structure activity relationships, to classify chemicals with little available data. Finally, the concept of using genomics to extrapolate from high to low dose effects was mentioned.

In summary, this workshop outlined some of the challenges in risk assessment and explored ideas for using toxicogenomics technologies to address them. The challenges and a general risk assessment background will be elaborated on in an upcoming report summarizing the workshop. The workshop report will be posted on the website of the standing Committee on Emerging Issues and Data on Environmental Contaminants: <http://dels.nas.edu/emergingissues/index.asp>. Currently, PowerPoint presentations and audiofiles of the talks are available on the website, covering the topic in much greater detail. 

**Do you want more information? Please visit our website at <http://dels.nas.edu/emergingissues/index.asp> where we have presentations from previous meetings, agendas for upcoming meetings, a current list of committee members, and other items of interest.**

**The committee’s fall meeting will focus on the use of toxicogenomics information in applying animal data to human health. If you would like to discuss this topic or suggest topics for consideration in our online forum, please see <http://dels.nas.edu/emergingissues/index.asp>.**

# National Toxicology Program Develops Its Vision for Twenty-First Century

The National Toxicology Program (NTP), part of the National Institute of Environmental Health Sciences, was established in 1978 to conduct toxicity testing on environmental contaminants. Its mission was and continues to be to collect, generate, and communicate information about potentially hazardous substances to improve and protect public health. To achieve its mission, the NTP provides toxicological evaluations, develops and validates new testing methods, assesses approaches and data for risk assessments, and communicates with a broad range of stakeholders (government, public, industry, academia, environmental community) who are interested in disease prevention and public health decision-making.

In order to stay in the forefront of toxicological issues, NTP is developing its *Vision for the 21<sup>st</sup> Century*. The goal of the vision is “to move toxicology from a predominantly observational science at the level of

disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.” To do this, NTP must actively incorporate new laboratory methods into its testing programs and insure that the resulting data meet the highest quality standards, and it must develop strategies to integrate new types of scientific data such as microarrays, into the decision-making process. As the science of toxicology advances, NTP will be challenged to use these new techniques and data to not only determine the toxicity of a chemical but to also understand the underlying mechanisms by which the toxic response occurs. The transition from traditional toxicity methods to the new technologies must be carefully done to ensure that public health is not jeopardized while the change occurs and that great uncertainty is not the unexpected result. Finally, NTP must identify the resources it will require to achieve both its short-term and long-term goals.

During 2004, NTP is interested in hearing comments from all stakeholders as it develops its implementation roadmap for the vision. Public input on questions such as the following are encouraged:

- What scientific information should the NTP be producing and what technical capabilities should the NTP have by 2008? By 2013?
- How do you envision that the refinement/replacement of classical toxicological studies with mechanism-based assays will impact on the evaluation of public health hazards?
- How can we best structure the NTP to provide this information and to ensure its optimal utilization in the protection of public health?
- What resources will be needed to realize this vision and how long will it take?

Those wishing to provide input to NTP on its vision or these questions may contact them at (919) 541-0530 or [liaison@starbase.niehs.nih.gov](mailto:liaison@starbase.niehs.nih.gov).

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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. The views expressed in the articles in this newsletter are those of the individual authors and do not reflect the findings or conclusions of The National Academies.*

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reports to the Pharmacology and Toxicology Coordinating Committee, a committee of CDER team leaders and senior management. The subcommittee has evaluated several voluntary submissions of genomic and ancillary toxicology data from pharmaceutical companies on compounds not undergoing regulatory review and has gained experience in the use of a reference toxicogenomics database to interpret genomic data. The subcommittee is using this experience to formulate recommendations for genomic data content and quality control metrics that would be useful for evaluating nonclinical pharmacogenomic submissions. Voluntary genomics submissions from industry have been and will continue to be a useful tool that helps both researchers and regulators gain experience in reviewing and analyzing toxicogenomics data and developing guidelines for the submission and review of these data.

The FDA recognizes that incorporation of standards and other measures of assay performance into

toxicogenomic data submissions could help assure regulators that high quality data are being submitted to support a regulatory review. To this end, FDA researchers and statisticians have initiated a collaborative research project to test the feasibility and value of using a set of mixed tissue samples to evaluate the ability of different laboratories and microarray platforms to detect designed-in differences in gene expression between two complex biological samples. FDA scientists are also participating in the External RNA Control Consortium (<http://www.cstl.nist.gov/biotech/workshops/ERCC2003/>) to develop universal external controls for gene expression analysis with microarrays and reverse transcription polymerase chain reaction assays. In addition, the FDA is working with the International Life Sciences Institute (ILSI), Health Level 7, Clinical Data Interchange Standards Consortium (CDISC), and other groups to establish electronic data standards for the capture and exchange of toxicogenomic data. 

## ***In the News:***

**The March 2004 issue of *Environmental Health Perspectives Toxicogenomics* includes a special section on Mechanism-Based Risk Assessments**  
<http://ehp.niehs.nih.gov/txg/docs/2004/112-4/toc.html?section=toxicogenomics>.

**The FDA's National Center for Toxicological Research (NCTR) has developed ArrayTrack, an integrated software system for managing, mining and visualizing microarray gene expression data, that you can run on your local machine.**  
<http://edkb.fda.gov/webstart/arraytrack/>.

**The NAS is holding an Arthur M. Sackler Colloquium on The Biology of RNAi, organized by Phillip Sharp and Andrew Fire**  
**National Academy of Sciences, Washington, DC**  
**May 17-18, 2004**  
<http://www.nas.edu/nas/colloquia>.

**Thursday Morning** (9:00 AM – 12:00 PM)

Introduction to Workshop

**Mark A. Rothstein**, Workshop Chair,  
University of Louisville  
**Robert Griffin**, Committee Member,  
Marquette University

Overview of Toxicogenomics

**William Greenlee**, Committee  
Member, CIIT Centers for Health  
Research

*Panel 1: Toxicogenomics communication and individual decision-making*

Possible discussion topics include: How do individuals use information to make decisions about risk? What psychological factors influence these decisions? What types of information are most useful? How is scientific information communicated to individuals and what do individuals need to communicate to scientists?

**Sharon Dunwoody**, University of Wisconsin  
**David Ropeik**, Harvard University  
**Julie Downs**, Carnegie Mellon University  
**Craig Trumbo**, University of Vermont

Panel discussion led by committee members **Patricia Buffler** and **Robert Griffin**

**Thursday Afternoon** (1:00 PM – 5:00 PM)

*Panel 2: Toxicogenomics communication and social deliberations*

Possible discussion topics include: How does individual risk perception get translated into societal decision making? How might toxicogenomic information impact social groups, such as susceptible populations, minorities, workers? Should there be equal access to this information?

**William Freudenburg**, University of California, Santa Barbara  
**Susanna Hornig Priest**, Texas A&M  
University  
**Deirdre Lawrence**, National Cancer Institute  
**K. Viswanath**, Harvard School of Public  
Health

Panel discussion led by committee members **Linda Fentiman** and **William Greenlee**.

Summary discussion with all panel members.

# Communicating Toxicogenomics Information to Non-Experts: A Workshop

Thursday, April 22, 2004

**NAS Building, 2101 Constitution Ave, NW  
Lecture Room**

**Washington, DC 20418**

**(Please Note New Location)**

**Have suggestions for newsletter topics? Want more information on the upcoming workshop? Email Jennifer Saunders at [jsaunders@nas.edu](mailto:jsaunders@nas.edu).**

Committee on Emerging Issues and Data on Environmental Contaminants  
Board on Environmental Studies and Toxicology  
Board on Life Sciences  
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**An Invitation to  
Communicating Toxicogenomics  
Information to Non-Experts:  
A Workshop**

APRIL 22, 2004

NAS Building, 2101 Constitution Ave, NW  
Lecture Room  
Washington, DC 20418

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