

## Using Toxicogenomics for Cross-Species Extrapolation

Do laboratory animals react to chemicals in the same way that humans do? The practice of toxicology is based on the presumption that in many cases they do. Can toxicogenomics lead to better predictions about whether humans will have the same reaction to a chemical as a laboratory animal? These issues were the focus of a one-day workshop held by the National Academies' standing Committee on Emerging Issues and Data on Environmental Contaminants on August 12, 2004 in Washington, DC. The workshop provided a forum for scientists, stakeholders, the regulated community and regulators to explore some of the scientific challenges and promises of applying toxicogenomics information to extrapolations from animal data to human health.

N. Leigh Anderson, of the Plasma Proteome Institute, and David Eaton, University of Washington, introduced the workshop by explaining that although animal models are traditionally used in toxicology as predictors of human response, there are many examples where animals and humans have different responses to a chemical or have a very different dose-response relationship. With advances in toxicogenomics, it is hoped that some of this variability may be anticipated and more accurate animal models developed.

Part of the impetus for this workshop came from a joint Society for Environmental Toxicology and Chemistry-Society of Toxicology Pellston workshop on cross species extrapolation that was held in July 2004. Dr. Richard Di Giulio, Duke University, one of the workshop organizers, said that among the conclusions reached by the participants was that genomic and computational approaches hold great promise for improving the science of cross-species extrapolation and for significantly improving human health and ecological risk assessments in the long run. The participants also found that 'omics technologies were unlikely to replace traditional toxicological methods in the foreseeable future, standardized approaches for conducting and analyzing experiments are needed, databases should be devel-

oped for surrogate species 'omics data, and considerable work will be required to link 'omic responses to adverse effects seen in animals.

The use of cross-species 'omics information for regulatory purposes was discussed by William Benson, U.S. Environmental Protection Agency (EPA), based on the EPA paper "Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA" (see newsletter issue 6 available at [www.dels.nas.edu/emergingissues](http://www.dels.nas.edu/emergingissues) for more information on the paper). He stressed that 'omics information on mechanisms of action and biological pathways might increase confidence in cross-species comparisons if it was known that a specific pathway occurred in humans and wildlife along with the respective surrogate test species. EPA's Computational Toxicology Program is attempting to improve quantitative risk assessment by taking such an approach.

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# From the New Committee Chair...

Kenneth S. Ramos, University of Louisville

The Standing Committee on Emerging Issues and Data on Environmental Contaminants (the Committee) was constituted by the National Academies at the request of the National Institute of Environmental Health Sciences, to provide a public forum for communication among government, industry, environmental groups, and the academic community about emerging issues in the environmental health sciences. At present, the scope of the Committee is focused on toxicogenomics and its applications in environmental and pharmaceutical safety assessment, risk communication, and public policy.



for his many contributions to the success of our efforts and look forward to tapping further into his experience and wisdom. As the Committee moves forward, we need to continue working as a group that is ready to serve the Academies, government agencies, and the scientific community, as a resource on emerging issues and technologies in environmental health sciences. Our role as a “think tank” able to catalyze high-energy discussions and the free flow of ideas as well as advance the research agenda will depend on that.

The Committee has worked towards achieving its objectives in part by organizing a series of workshops on toxicogenomics. An inaugural symposium in November, 2002 and a workshop in February, 2003 were held to acquaint participants with the state-of-the-science and organized efforts to advance the research agenda in toxicogenomics. These meetings were followed with four workshops focusing on bioinformatics, risk assessment, risk communication, and cross-species extrapolations. Workshop summaries on risk assessment, risk communication, and cross-species extrapolation will soon be published. A major objective of these workshops has been the creation of a forum for stakeholder discussion of issues of common concern and identification of areas of priority for further Committee action. The format has further evolved to foster continued dialog among federal agencies and the committee and to make such dialogs an integral part of the workshops themselves.

During the next year, the Committee will continue to promote efforts to maximize dialog among scientists, regulators, government officials and the public on toxicogenomics, its applications in safety risk assessment, and unrealized opportunities in public health and product development. The primary agenda item for the January 4-5, 2005 meeting will be identification of priority areas for the Committee. Setting the working agenda for the next year will require meaningful involvement of committee members, the federal liaison group and other stakeholders. We will benefit from the contributions of several new committee members with expertise in pharmaceutical development, marketing, law, public health, and the European chemical industry, as well as new perspectives from academic scientists conducting toxicogenomics research. As such, it is with considerable enthusiasm that I look forward to working with each of you as we continue this venture, and look forward to input from all of our stakeholders as we roll out the working agenda for the year ahead.

The Committee also developed a proposal for a National Research Council study on toxicogenomics, to be undertaken by a separate and independent committee on “Applications of Toxicogenomics Technologies to Predictive Toxicology”. This committee will evaluate the potential short- and long-term scientific applications of toxicogenomics, and the challenges of using toxicogenomics in environmental and pharmaceutical risk assessment. The report produced by this committee will identify critical issues for realization of the scientific potential of toxicogenomics.

As the first Standing Committee turns over and we thank departing members for their contributions and welcome new members, I would like to recognize David Eaton’s leadership during a period of self-definition and evolution for the Committee. We are indebted to him

*Kenneth S. Ramos, University of Louisville Health Sciences Center, is the new chair of the Committee on Emerging Issues and Data on Environmental Contaminants. His appointment follows completion of David Eaton’s term in August, 2004.*

# Using Toxicogenomics for Cross-Species Extrapolation

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The committee recognized that the use of ‘omic technologies for cross-species extrapolations is still in its infancy, but asked workshop speakers to speculate on how these technologies might be applied in the future. Frank Witzmann, Indiana University, addressed the technological challenges of using proteomic information to look at responses to toxic agents in various animal species. He noted that determining whether an animal’s in vivo proteome response is mimicked by in vitro systems will be critical to further validating cross-species extrapolations.

Donna Mendrick of Gene Logic, provided a practical example of using toxicogenomics to improve cross-species extrapolation. Her company is using omics information to see if pathological responses to a chemical are species specific and whether they are relevant to humans. She presented a case study in which gene transcription was compared in the liver of two species to see if they responded the same way to a chemical and if either species appeared to be a better predictor of possible human toxicity.

The use of metabonomics for discerning species differences was discussed by Susan Sumner of Paradigm Genetics, Inc. She emphasized that metabonomics has an advantage over other methods because it typically analyzes body fluids such as urine, and therefore biomarker profiles developed in studies using laboratory animals can be extrapolated for use in human studies. Metabolomic-based biomarkers can be used to identify which biological pathways are involved in a response (exposure or disease) to a chemical in different species, and because biochemical pathways are, in general, conserved across mammals, metabonomics provides one avenue for cross-species comparisons. Metabonomics can be applied in research areas such as the study of age, gender, genetic make-up, or disease staging.

One of the most talked about but possibly least understood areas of the genomic sciences is systems biology. Russell Thomas of the CIIT Centers for Health Research, defined systems biology as “the quantitative description of an organism from the assembly of individual components into subsystems of increasing complexity and organizational hierarchy.” Understanding the

molecules in the network and their quantitative interactions might provide insights into how well a given response is conserved across species.

Stephen Nesnow, EPA, described work at the National Health and Environmental Research Laboratory to understand species differences in the carcinogenic effects of the antifungal triazole-containing conazoles. Nesnow and colleagues are using traditional toxicological methods combined with toxicogenomics to study the mechanism of action of these chemicals and to examine the toxicological differences between rats, mice, and humans to determine if there is a common underlying biochemical event. They seek specific genes and pathways that are affected by the conazoles and perhaps are responsible for the observed cross-species differences.

One of the chemicals receiving considerable scrutiny these days is perfluorooctanoic acid (PFOA), which elicits unusual responses in different species and genders. John Butenhoff, 3M Corporation, is conducting studies to determine whether pharmacokinetics is driving the sex and species response differences. Butenhoff believes that differential expression of one family of proteins, the organic anion transporters, may be responsible for some of the different effects seen in response to PFOA and that ‘omic technologies may be valuable for exploring how these proteins are expressed.

Following the presentations, workshop attendees participated in a roundtable discussion of the use of toxicogenomics technologies to improve cross-species extrapolations and thus improve human-health risk assessments. Among the many topics touched upon, mode of action, commonality of pathways between species, other types of extrapolations, and uncertainty factors all received considerable attention. Many workshop participants believed that toxicogenomics might provide insights in each of these areas, whether by supplementing traditional methods such as showing whether signaling pathways are conserved across species, elucidating possible modes of action among species, helping to determine species differences at high and low doses, or reducing the use of uncertainty factors when extrapolating from laboratory animals to a diverse human population.

**Would you like more information? Please visit our web site at <http://dels.nas.edu/emergingissues> where we have presentations and audio files from previous workshops and meetings, newsletters, agendas for upcoming meetings, a current list of committee members, and other items of interest.**

# Emerging Molecular and Computational Approaches for Cross-Species Extrapolations: A Workshop Summary

By William H. Benson , Environmental Protection Agency  
and Richard T. Di Giulio, Duke University

Advances in molecular technology have led to the elucidation of full genomic sequences of several multicellular organisms, ranging from nematodes to man. The related molecular fields of proteomics and metabolomics are now beginning to advance rapidly as well. In addition, advances in bioinformatics and mathematical modeling provide powerful approaches for elucidating patterns of biological response imbedded in the massive data sets produced during genomics research. Thus, changes or differences in the expression patterns of entire genomes at the levels of mRNA, protein and metabolism can be assessed rapidly. Collectively, these emerging approaches may greatly enhance our ability to address many of the major issues in human and environmental toxicology. Specifically, they are uniquely qualified to address the issue of cross-species extrapolation in risk assessment in both human and environmental toxicology.

Although there may be important differences in the genomes and proteomes among species, many of the responses to various stressors are evolutionarily conserved. For example, consider how fish, birds, and mammalian species respond to external stressors, including chemical toxicants (both synthetic and natural), genotoxicants (carcinogenic or mutagenic), or parasites. Stressed organisms can initiate both defensive and offensive actions to counteract adverse responses. Many of these defensive responses to external stimuli are common to many organisms, including wildlife species (fish, birds, invertebrates) and humans. Genomic technologies may provide great insight into how diverse organisms respond to environmental stressors.

Motivated by these concerns, the Society of Environmental Toxicology and Chemistry (SETAC) and the Society of Toxicology (SOT) jointly sponsored a workshop entitled "Emerging Molecular and Computational Approaches for Cross-Species Extrapolations" in Forest Grove, Oregon, USA from 19 to 22 July 2004. This workshop was significant because leading societies - concerned on the one hand with the integrity of the environment (SETAC) and on the other hand with the improvement of human health (SOT) - worked together. Thirty-five scientists and professionals were brought together from diverse fields including environmental toxicology and chemistry, biomedical toxicology, molecular biology, genetics, physiology, bioinformatics, computer science and statistics. Such collaboration provided an ideal vehicle for objective and balanced discussion

of this topic among professionals from different yet highly inter-related disciplines. The overall goal of the workshop was to outline a research agenda utilizing emerging technologies in omics and computational biology in order to: 1) elucidate similarities and differences among species, 2) relate stressor-mediated responses to adverse outcomes, and 3) extend this science into innovative approaches to risk assessment and regulatory decision-making.

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## Coming Soon:

**"Communicating Toxicogenomics Information to Nonexperts: A summary of a workshop" will soon be available on the committee's web site:**

**<http://dels.nas.edu/emergingissues>.**

Communicating technical information to the public about a developing science, such as toxicogenomics, can be challenging, particularly when the applications of that science are not yet well understood. As the technology develops and more data become available, it is important that scientists and the public discuss the promises and limitations of this new field. On April 22, 2004, the Committee on Communicating Toxicogenomics Information to Nonexperts held a workshop to consider issues in and strategies for communicating toxicogenomics information to the public and other nonexpert audiences.


# Emerging Molecular and Computational Approaches for Cross-Species Extrapolations: A Workshop Summary

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Workshop participants identified specific research gaps and emerging issues. Key conclusions and recommendations workshop were:

- Genomic technologies provide powerful research tools, but are currently insufficient as a basis for risk assessment and replacement of traditional approaches.
- Perform collaborative proof of concept studies to improve our understanding of cross-species extrapolation by characterizing similarities and differences in metabolic pathways.
- Develop more standardized approaches for omics technologies and associated data analysis.
- Develop genomic databases for selected surrogate species, focusing on basic, conserved cellular and physiologic processes.
- Perform studies to validate relationship between omics responses and adverse biological outcomes.
- Form a standing task force for cross-species/genomic issues.
- Enhance training in genomic technologies, particularly within the context of an interdisciplinary approach.

All relevant discussions and conclusions from the workshop will be published in a book edited by William H. Benson and Richard T. Di Giulio, and published through SETAC Press as was a previous SETAC-SOT Workshop which focused on interconnections between human health and ecological integrity (Di Giulio and Benson, 2002). The conclusions and recommendations from the 2002 workshop on human health-ecological integrity served as the basis for the workshop on computational approaches and cross-species extrapolations.

Di Giulio, R.T. and W.H. Benson (eds.). 2002. *Interconnections Between Human Health and Ecological Integrity*. SETAC Press, Pensacola, FL. 

The SETAC-SOT Workshop was sponsored by:

- National Institute of Environmental Health Sciences
- National Oceanic and Atmospheric Administration
- Pfizer, Inc.
- The Procter and Gamble Company

## “Hold the Date”

### Public Databases: Sharing of Toxicogenomic Data

**March 10, 2005, 12:30 to 5:00 PM**

This session will be held in New Orleans immediately following the Society of Toxicology meeting, exact room location to be announced.

The National Academies standing Committee on Emerging Issues and Data on Environmental Contaminants is holding an open meeting to discuss the use and sharing of toxicogenomic data in a public database. Sharing data through publicly accessible databases would expedite scientific progress, but a variety of impediments exist that limit such data sharing. This forum will seek to identify these impediments and discuss strategies to overcome them.

More information, the latest agenda, and registration will be available at <http://dels.nas.edu/emergingissues>. Assuming space is available, non-registrants are welcome to attend.

# Members of the Committee on Emerging Issues

*As of September 2004 terms of service expired for several committee members. New members have been appointed as noted below*

**Kenneth S. Ramos**, (Chair), University of Louisville Health Sciences Center, focuses on the study of molecular mechanisms of environmental disease and redox-regulated transcriptional control.

**N. Leigh Anderson**, Plasma Proteome Institute, has worked in proteomics, pioneering a range of applications in drug discovery, toxicology, and surrogate markers.

**Patricia A. Buffler**, University of California, Berkeley, has research interests that include the environmental causes of cancer, especially gene-environment interactions; epidemiologic research methods; and the use of epidemiologic data in health policy.

**James S. Bus**, Dow Chemical Company, directs research on the pharmacokinetics of industrial chemicals and pesticides and its relationship to mechanisms of chemical toxicity.

\***Joseph DeGeorge**, Merck Pharmaceuticals, works on safety assessment of drugs. He has also worked on drug evaluation at the FDA.

**Georgia M. Dunston**, Howard University, conducts research on the biomedical significance of population-based DNA sequence variation.

**David L. Eaton**, University of Washington, is studying the molecular basis for environmental causes of cancer and how genetic differences affect susceptibility to environmental agents.

**Linda E. Greer**, Natural Resources Defense Council, has focused on toxic chemical evaluation and regulation, and policy decision-making through risk assessment.

**Robert J. Griffin**, Marquette University, teaches and conducts research on communication about environmental issues, energy, health, and risk.

**John D. Groopman**, Johns Hopkins University, is conducting research on molecular biomarkers for environmental carcinogens and molecular epidemiology.

**Casimir A. Kulikowski**, Rutgers University, has research interests that include bioinformatics, medical informatics, and artificial intelligence.

\***Amy Kyle**, University of California, Berkeley, focuses on the development of environmental health indicators, policy responses, and risk assessment in U.S. environmental policy.

**Philip Leder**, Harvard Medical School, is focusing on the molecular genetics of malignancy and the molecular genetic approach to pattern formation in the mouse embryo.

\***Peter Lord**, Johnson & Johnson, conducts research focusing on the application of molecular biology, particularly toxicogenomics, to the drug safety evaluations and toxicological risk assessment.

\***William B. Mattes**, Gene Logic, Inc., works in quantitative assays for transcript profiling, bioinformatics, cross-species comparisons, and transcript changes as a function of dose and time.

\***George Orphanides**, Syngenta CTL, works in toxicology, with specific interests in toxicogenomics, including gene expression profiling and proteomics.

**Frederica Perera**, Columbia University, works on the environmental causes of disease, molecular epidemiology, children's risk, and environment-susceptibility interactions in cancer.

**John Quackenbush**, The Institute for Genomic Research, works in functional genomics and bioinformatics, animal models of human disease, and software development for microarray expression analysis.

**Mark A. Rothstein**, University of Louisville, works in the areas of ethical, legal, and social implications of genetics, privacy, health policy, and employment law.

\***Leona Samson**, Massachusetts Institute of Technology, has focused on how cells, tissues, and animals respond to environmental agents, using cell genetics and genomics including transgenic and knockout technologies.

\***Peter Spencer**, Oregon Health and Science University, conducts research in cellular relationships in the nervous system, and the actions of neurotoxic chemicals in human disease.

\***Lawrence Sung**, University of Maryland, works on intellectual property law, biotechnology and technology transfer.

**Cheryl L. Walker**, University of Texas M.D. Anderson Cancer Center, is examining the genetic basis of susceptibility to cancer, molecular mechanisms of carcinogenesis, and the effects of hormones on gene expression.

**Russell D. Wolfinger**, SAS Institute, Inc., works in genetic data analysis and assessing gene significance from microarray data via mixed models.

\* Indicates new committee member as of September 2004.

# Committee on Emerging Issues and Data on Environmental Contaminants

## Meeting 8

You are welcome to attend the January 4<sup>th</sup> open session of the Committee on Emerging Issues and Data on Environmental Contaminants. This will not be a workshop on a particular topic but rather a time for the Committee to discuss issues and priorities for workshops and forums to take place in the next 1-2 years.

Participants are expected from the National Institute of Environmental Health Sciences (NIEHS), federal agencies with interests in toxicogenomics, and researchers working in the field.

This session will not be webcast. More information will be available at <http://dels.nas.edu/emergingissues> or contact Jordan Crago at [jcrago@nas.edu](mailto:jcrago@nas.edu) or 202-334-1790.

**TUESDAY, JANUARY 4, 2005**

**1:00 PM to 5:30 PM  
Open Session**

**The National Academies  
Keck Center  
500 5th Street, NW  
Room 101  
Washington, DC 20001**

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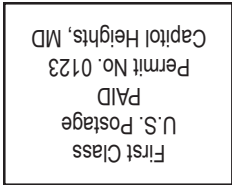
Jordan Crago

#### Newsletter

Jordan Crago

*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.*



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  
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## Meeting of Committee on Emerging Issues and Data on Environmental Contaminants

**TUESDAY, JANUARY 4, 2005**

**The National Academies  
Keck Center  
500 5th Street, NW  
Room 101  
Washington, DC 20001**

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