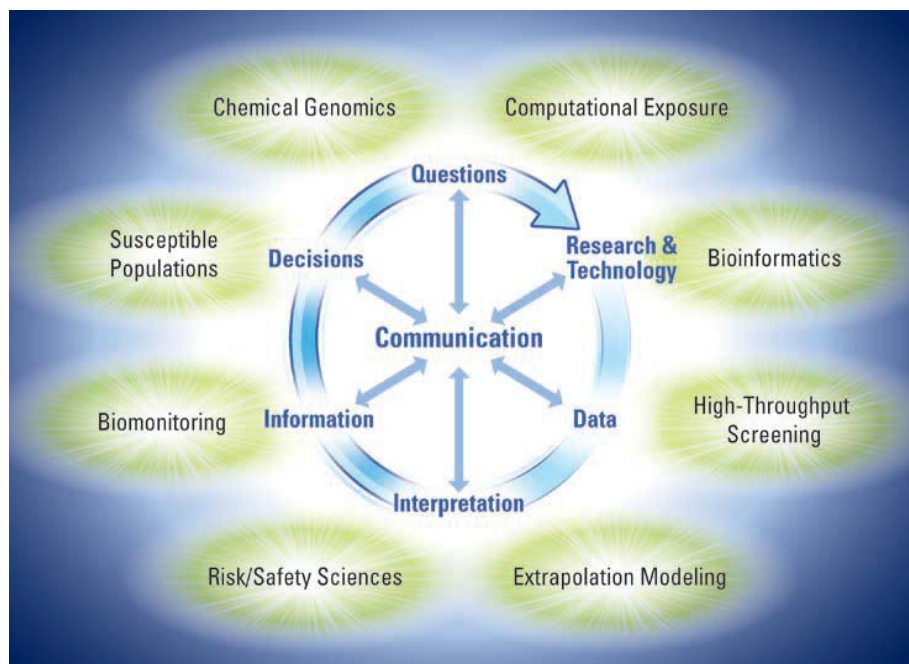


**International Council of Chemical Associations (ICCA)  
Long-Range Research Initiative (LRI)**



**Connecting Innovations in Biological,  
Exposure and Risk Sciences: Better  
Information for Better Decisions  
Workshop Summary Report**

**June 16 and 17, 2009  
Charleston Place Hotel  
Charleston, South Carolina, United States**



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**September 28, 2009**

## Contents

Organizing Committee Members.....	ii
List of Acronyms .....	iv
About the ICCA-LRI .....	v
<b>Executive Summary</b> .....	vii
<b>1.0 Introduction</b> .....	1
<b>2.0 Opening Session</b> .....	2
2.1 The Context for the Workshop .....	2
2.2 Setting the Stage for the Breakout Sessions .....	4
<b>3.0 Breakout Sessions</b> .....	7
3.1 Session 1: Advanced Technologies .....	7
3.2 Session 2: Exposure Science .....	13
3.3 Session 3: Communication .....	19
<b>4.0 Actualizing Innovations in Biological, Exposure, and Risk Sciences</b> .....	26
<b>5.0 Summary</b> .....	28
<b>6.0 References</b> .....	30
Appendix A: Participant Affiliations .....	A-1
Appendix B: Final Agenda .....	B-1
Appendix C: List of Poster Presentations .....	C-1

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## List of Acronyms

ACC	American Chemistry Council
BPA	bisphenol A
CDC	Centers for Disease Control and Prevention
Cefic	European Chemical Industry Council
DBP	dibutyl phthalate
DDT	dichlorodiphenyltrichloroethane
DNA	deoxyribonucleic acid
ebCTC	Environmental Bioinformatics and Computational Toxicology Center
EC <sub>50</sub>	half maximal effective concentration
ED <sub>50</sub>	effective dose producing a response in 50 percent of the population
FDA	U.S. Food and Drug Administration
FP6	6th European Union Framework Programme for Research and Technological Development
GEI	Genes, Environment, and Health Initiative
GPS	Global Product Strategy
HTS	high-throughput screening
ICCA	International Council of Chemical Associations
JCIA	Japan Chemical Industry Association
LRI	Long-Range Research Initiative
MICA	Mechanistic Indicators of Childhood Asthma
miRNA	micro ribonucleic acid
MOA	mode of action
NCGC	National Institutes of Health Chemical Genomics Center
NCS	National Children's Study
NERL	National Exposure Research Laboratory
NewGeneris	Newborns and Genotoxic Exposure Risks Project
NHANES	National Health and Nutrition Examinations Survey
NIH	National Institutes of Health
NRC	National Research Council
NTP	National Toxicology Program
PBPK	physiologically-based pharmacokinetic
PBDE	polybrominated diphenyl ether
PCBs	polychlorinated biphenyls
PXR	conazole-pregnane X receptor
qHTS	quantitative high-throughput screening
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD	reference dose
RNA	ribonucleic acid
SNPs	single nucleotide polymorphisms
U.S. EPA	U.S. Environmental Protection Agency
USA	United States of America

## About the ICCA-LRI

The International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) comprises three regional LRI programs that are independently managed by the American Chemistry Council (ACC), the European Chemical Industry Council (Cefic), and the Japan Chemical Industry Association (JCIA) (see [www.icca-chem.org](http://www.icca-chem.org)). The primary aim of the ICCA-LRI is to provide a scientific foundation that can enable the chemical industry as part of the larger global society to make responsible product stewardship and regulatory decisions concerning the production, marketing, and use of its products. Substantial progress towards this aim has been realized through the strong commitment by each of the ICCA regional programs to the greater LRI vision.

ICCA-LRI projects are implemented in cooperation with the scientific community and governmental institutions and the results are published and shared freely with the public, regulators, industry, and the academic and governmental communities. For this reason, the ICCA-LRI has developed research and communication strategies that link with outreach activities to governments, non-governmental organizations, and the public. A key component of the communication and outreach strategies has been a series of public workshops (see ICCA-LRI Workshops List at right) that focused on integrating the challenges of biomonitoring with broader issues such as toxicity testing, exposure assessment, and new methodologies for risk assessment. These workshops were designed to complement ongoing research, ensure coordination in implementation of regional ICCA-LRI research programs, continue engagement with public authorities, and provide leadership to others working in the research field.

### Overview of ICCA-LRI Workshops

**2005 - Workshop on Human Biomonitoring - Paris, France.** Examined biomonitoring from the perspectives of product stewardship, policy/advocacy, communication, and existing scientific knowledge gaps.

**2006 - Making Sense of Human Biomonitoring Data - Minneapolis, Minnesota, USA.** Fostered consensus on priorities for future research in biomonitoring for ICCA-LRI and other research organizations.

**2007 - Public Health Applications of Human Biomonitoring - Research Triangle Park, North Carolina, USA.** Provided a venue for discussions about the strengths and weaknesses of biomonitoring for the purposes of public health tracking, intervention, and protection.

**2008 - Twenty-First Century Approaches to Toxicity Testing, Biomonitoring, and Risk Assessment - Amsterdam, The Netherlands.** Addressed advances in the new technologies for toxicity testing and biomonitoring; considered approaches for effective communication of the deluge of data from these new technologies; and promoted exchange of views on how these technological advancements can be used to improve the science of human health risk assessment.

Through its biomonitoring research program, the ICCA-LRI recognized that the relationships among biomonitoring, real-world exposures, and recent innovations in technology for toxicity testing could be synergized through a globally coordinated effort by LRI. Such an effort could provide great value to the chemical industry by improving understanding of the

potential effects of chemicals at environmentally relevant exposure levels. As a result, a new research direction—modernizing methods for risk assessment—emerged from the biomonitoring work. Through this new effort, ICCA-LRI is taking a lead in fostering innovative approaches for the assessment of risk with the goal of improving our understanding of dose, exposure, and ultimately the risks associated with environmental stressors.

## Executive Summary

The International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) held its 2009 Workshop, *Connecting Innovations in Biological, Exposure and Risk Sciences: Better Information for Better Decisions*, on June 16 and 17, 2009 in Charleston, South Carolina, USA. More than 100 participants from government, academia, non-governmental organizations and industry representing 15 different countries attended the workshop, the fifth in the ICCA-LRI annual series.

Assessing complex human health risks requires data that clearly characterize the hazard, the exposure conditions, the exposed populations and the relevant susceptibility factors to identify risks among different populations. A key driver for this workshop was to understand how recent advances in biological technologies can be harnessed to identify hazard and, more importantly, to characterize risks from exposures to chemicals. This focus stimulated discussions about the exposure information that is needed to inform the design of risk assessment studies. The discussions also highlighted the importance of interpreting the volumes of data emerging from the new technologies in ways that are relevant to the chemical exposures experienced by human populations. A cross-cutting theme for the workshop discussions was better understanding of genetic influences and gene-environment interactions regarding the effects of chemical exposures with a focus on improved risk assessment for susceptible populations. As the science continues to evolve, new tools will be required to effectively communicate the findings and what they may mean to all stakeholders throughout the research and decision-making processes.

Findings from the workshop are detailed in this report; key findings include the following:

- Advanced technologies and the 'omics' offer great promise as alternatives to traditional toxicity testing strategies. Genomic tools are rapidly evolving and have the potential to dramatically change how chemical risk assessment is done; however, integration and interpretation of the new data using bioinformatic tools remain as key challenges.
- Accurate assessment of real-world environmental exposures is an outstanding and largely unmet challenge that must be resolved to produce meaningful toxicological information that can appropriately inform risk assessments.
- Establishment of trust among scientists, stakeholders and decision-makers is a fundamental priority for fostering acceptance of research results from the new technologies.
- Communicating the relevant findings from the deluge of new scientific data to the public and to involved stakeholders is a current challenge. Effective communication of the results from the complex data sets will be essential for building trust among stakeholders.
- Making sense of the emerging data requires integration of heterogeneous types of information and knowledge across many disciplines – building capacity for trans-disciplinary research will be essential.
- Data from exposures in the low-dose range are needed to improve our understanding of biological responses to everyday exposures to chemicals and activation of response pathways in cells and organisms across the dose-response continuum.
- Risk and health assessment systems must evaluate and account for genetic variability among populations and relate this variability to exposure. Variability between individuals

and among populations, as well as differences in susceptibility due to age or health status, can also contribute significantly to variation in risks related to chemical exposures.

- Cumulative and integrated exposure assessments for chemicals are emerging as a new norm; this thinking must be considered and incorporated into the exposure assessment component during design of risk assessment strategies.
- Statistical tools are available to optimize exposure data collection and analysis – all data points need not be collected from each individual to develop the exposure landscape. Application of appropriate statistical methods to the data generated by the exposure assessment is essential.
- ‘Omics’ can provide important new tools for exposure assessment to improve understanding of the global biological landscape.
- Communication frameworks must integrate risk-benefit perspectives and incorporate cultural and value differences if they are to effectively deliver results from emerging research as well as explain their meaning to stakeholders and decision-makers.

ICCA-LRI workshops are designed to foster interactions among researchers and stakeholders, to stimulate discussions that can improve the scientific basis for policymaking and to support consensus building that can advance the risk assessment process for chemicals. As in previous years, the 2009 workshop provided a venue for highlighting ICCA-LRI as a leader and knowledge partner among scientific and regulatory experts. These workshops demonstrate the value of industry-sponsored science to directly address many of the complex scientific and regulatory challenges faced by the industry as it advocates for sound chemical management policies.

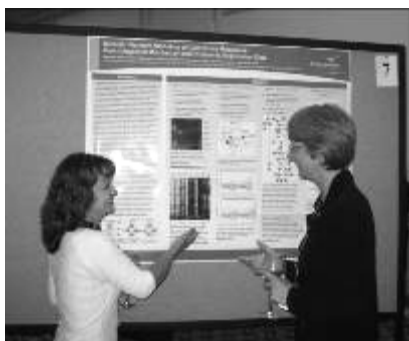


2009 ICCA-LRI Workshop  
Co-Chairs, Elaine Cohen  
Hubal, Environmental  
Protection Agency, USA and  
Richard Phillips, ExxonMobil  
Petroleum & Chemical,  
Belgium

## Snapshots from the 2009 ICCA-LRI Workshop



Elaine Cohen Hubal, U.S. EPA and Tina Bahadori, ACC, USA



Katrina Waters, Pacific Northwest National Laboratory, USA and Lesa Aylward, Summit Toxicology, USA



Corinna Weinz, Bayer AG, Germany



Scott Loveless, DuPont; James Bus, The Dow Chemical Company; and Stuart Cagen, Shell Health, USA (from left)



Peggy Geimer, Arch Chemicals; Kathleen Plotzke, Dow Corning Corporation; Brenda Barry, ACC; and Annette Guiseppi-Elie, DuPont, USA (from left)



Melanie Bausen, BASF – The Chemical Company, Germany



Timothy Gant, University of Leicester, UK; Matti Jantunen, National Institute for Health and Welfare, Finland; and Stephen Edwards, U.S. EPA, USA



Richard Becker, ACC; Janet Mostowy, ICCA-LRI Planning Group Chair, Bayer Corporation; and Steven Robison, Procter and Gamble Company, USA



Susan Blevins and Rosemary Zaleski, ExxonMobil, USA



Russell Thomas, The Hamner Institutes for Health Sciences; Justin Teeguarden, Pacific Northwest National Laboratory; and Katrina Waters, Pacific Northwest National Laboratory, USA (from l to r)



Nancy Wilson, Battelle, and Kimberly Osborn, ICF International, USA



Alexis Castrovinci and Ami Parekh, ICF International, USA

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## 1.0 Introduction

The International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) held its 2009 Workshop, *Connecting Innovations in Biological, Exposure and Risk Sciences: Better Information for Better Decisions*, on June 16 and 17, 2009 in Charleston, South Carolina, USA. A primary aim of the workshop was to stimulate discussions on approaches to translate the deluge of data emerging from recent advancements in biological technologies and bioinformatic sciences into information that is effective and useful for risk-based decision-making concerning risks from chemicals. More than 100 participants from government, academia, non-governmental organizations and industry representing different 15 countries attended the workshop, which is the fifth in this annual series.

The advent of new technologies, which include the 'omics' such as toxicogenomics, proteomics, metabolomics, and transcriptomics as well as bioinformatic sciences, presents an opportunity to develop a new paradigm for toxicity testing of chemicals. These recent scientific developments have the potential to facilitate better understanding of the health implications concerning exposures to chemicals for the general public. The workshop focused on the growing gap between advancements in the new technologies and the science to interpret and understand the emerging data. The three major themes for the workshop were advanced technologies, exposure science, and communication. A cross-cutting theme was understanding how genetic influences and gene-environment interactions may impact the effects of chemical exposures and using such information to improve health assessments among susceptible populations. Key questions for workshop participants included: what research is needed to bridge the current knowledge gap; how to harness the data to better inform decisions about public health; and how best to communicate research outcomes as they evolve.

The agenda for the two-day workshop, including the list of the speakers and titles of their presentations, is provided in Appendix B. Plenary session presentations during the first morning set the stage for additional presentations and discussions during parallel breakout sessions on the three workshop themes later in the day. A poster session during the evening of the first day showcased research from a variety of projects related to exposure modeling, biomarker analysis, use and interpretation of biomonitoring data, and mode of action (MOA) analysis for risk assessment. A list of the posters presented is included in Appendix C. The breakout sessions continued on the second morning and workshop participants then reconvened for the closing plenary presentations. The closing plenary session began with summaries of the deliberations and outcomes from the breakout sessions from rapporteurs who had attended the sessions. Additional plenary session presentations focused on actualizing the innovations in biological and exposure sciences and future directions for risk assessment.



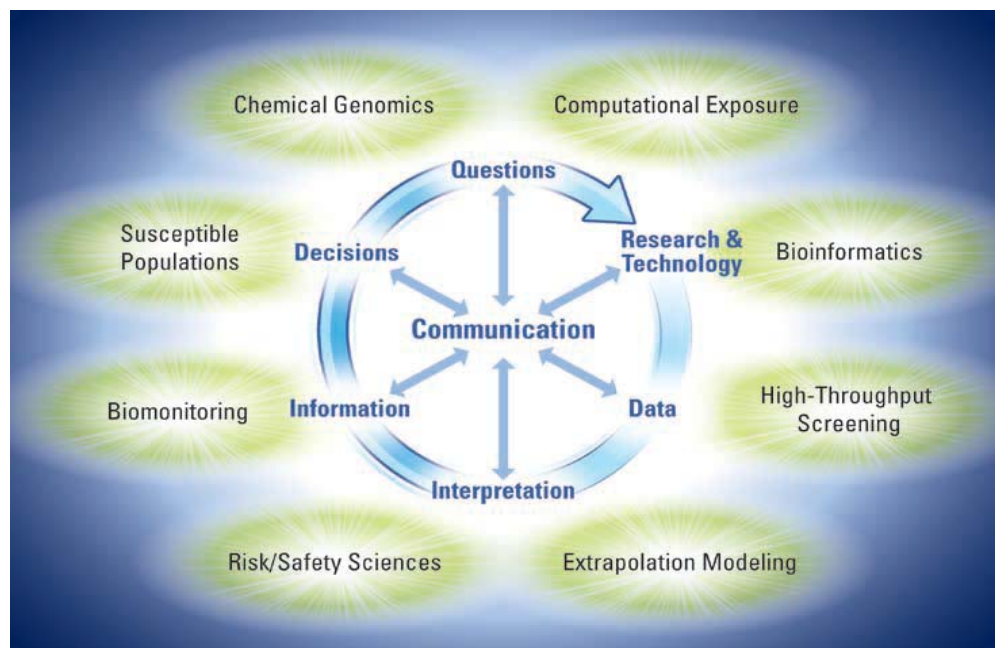
Elke Anklam, Institute for Health and Consumer Protection, Joint Research Centre, European Commission, Italy

The following is a summary of the presentations, discussions, and overarching themes for the plenary and parallel breakout sessions at this workshop.

## 2.0 Opening Session

Opening remarks for the workshop described how ICCA-LRI research programs are addressing the growing gap between advancements in new technologies and the science to interpret and understand the emerging data. Advancements in areas such as chemical genomics, computational exposure, bioinformatics, high-throughput screening, and extrapolation modeling are producing a deluge of data that will require meaningful interpretation and effective communication of the results so that they are useful for policymakers and other decision-makers. Figure 1 illustrates the key role of communication in all steps of the process, beginning with formulation of questions for the research that can include use of the new technologies to development of the regulatory decisions that can impact public health and the environment.

**Figure 1**  
**From Data to Decisions: Informing Regulatory Policy**



LRI research is designed to address the growing gap between advancements in the new technologies and the science to interpret and understand the emerging data.

## 2.1 The Context for the Workshop

Speakers in the opening plenary session were tasked with presenting their views on risk assessment and its role in meeting today's global challenges concerning human health and environmental issues. The first perspective provided by a representative from the European Commission outlined a number of important policy needs for human health risk assessment.

Examples included chemical safety for consumer products, information to support the safe use and handling of chemicals as is currently required under the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program, food safety issues, and environmental and human health concerns. As part of its contribution to policy development, the risk assessment process must consider information from a variety of sources, including available human and animal studies data, exposure data, and data from traditional toxicity testing as well as the emerging technology approaches. Current challenges for this process include limited exposure data, continuing efforts to reduce use of animals for testing, developing efficiencies in risk-benefit analyses and in comparative risk assessment, and focusing on reducing uncertainty in risk characterization and assessment. An overall goal is to increase cooperation among research programs in industry and at academic centers of excellence worldwide and to encourage integration of testing strategies across diverse resources towards meeting the global regulatory needs. The presentation concluded with an overview of the European Commission's Joint Research Centre and its directions towards integrating risk assessment methodologies, including the 'omics' technologies.



John Young, Ministry of Health, Israel

The presentation that followed from the U.S. Humane Society continued on the theme of reducing reliance on animal models for toxicity testing. It provided an historical perspective on these efforts and their alignment with previous development of the concept of the three R's, reduce, reuse, and recycle. A focus of the presentation was that new technologies offer the prospect to facilitate a shift away from animal models that could decrease traditional toxicity study durations and their high costs as well as the requirements for extrapolation of data from animal to humans. Recent activities by the U.S. Humane Society include efforts to increase public funding for three R's research and initiatives, including those involving the new technologies, support for incorporating three R's methods into international guidelines, and the development of a new Web site as forum for non-animal testing methods.

Exposure modeling in Israel was used as an example by the next speaker to consider how risk assessment findings can be applied to a greater global context. Information about different dietary regimes as well as lifestyle behaviors and residential living choices were compared among Israeli and non-Israeli populations to evaluate the impact of these factors on exposures among the various populations. Metabolic differences and genetic factors, such as polymorphisms, were also considered as important determinants in health outcomes that follow exposures.

As noted previously, effective communication about numerous aspects of the new technologies will be essential for their understanding, acceptance, and use by risk assessment practitioners, regulatory decision-makers and the general public. However, the natural human tendency to minimize or avoid change and a reluctance to welcome new technologies can hamper such acceptance. A speaker from the Cultural Cognition Project used nanotechnology,

another emerging new technology, as a case example to understand perceptions about risk for a variety of issues among individuals who were and were not familiar with nanotechnology. The presenter described two theories of risk perception: the rational actor theory purports that the more knowledgeable one is about a specific topic, the more accurate one is likely to be about its potential risks, and the cultural theory of risk perception maintains that one perceives risks in relation to one's prized commitments and these are reflected in the values expressed. The presenter described results from several studies indicating that perceived risks about topics ranging from genetically modified foods to the internet decreased with increasing knowledge about nanotechnology. This presentation underscored the key role of communication to provide credible information so that individuals can make informed decisions about possible risks.



Donald Braman, George Washington University Law School, USA

## 2.2 Setting the Stage for the Breakout Sessions

The presentations in this session provided overviews for the three workshop themes of advanced technologies, exposure science, and communication that would be explored in greater detail during parallel breakout sessions.

An overview of current challenges and directions for exposure science opened this session. An immediate challenge is to develop improved methods that will meet the mandate to evaluate the large numbers of environmental chemicals and their potential human health risks. As described in the 2007 National Research Council (NRC) report, *Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy*, new tools are available to examine toxicity pathways with a depth and breadth not previously possible (NRC, 2007). This NRC report has defined toxicity pathways as cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects. To meet the goal of screening chemicals for risk, the new technologies must be applied to assess the potential for both toxicity and exposure. High-throughput screening (HTS) approaches for toxicity testing and chemical prioritization have been accelerated through the advent of the Tox21 program, which was established through a memorandum of understanding among the National Toxicology Program (NTP) Biomolecular Screening Branch, the National Institutes of Health Chemical Genomics Center (NCGC) Toxicology Project Team, and the ToxCast™ program at the U.S. Environmental Protection Agency's (U.S. EPA) National Center for Computational Toxicology. A key question is how the emerging volumes of new information will be translated and used to assess potential human health risks from real-world exposures to chemicals. Population-based data and human exposure information are critical for guiding development and use of this toxicity information. Because assessment of complex human health risks requires that hazard, susceptibility, and exposure all be characterized reliably, advancing exposure science remains a critical need.

Key research questions in exposure science include what is required to properly characterize critical elements of exposure, including real-world exposure conditions and background exposure levels, and how can new scientific knowledge and tools in the molecular, computational, and information sciences be leveraged to develop rapid, inexpensive approaches

for characterizing biologically relevant exposures. A systems biology approach could be most advantageous because it considers exposures at all levels of a biological organism. This approach could include coupled networks that span multiple levels of biological organization and extend to network analyses that can inform risk assessment. As a parallel to ToxCast™, ExpoCast™ has been introduced as a new U.S. EPA program. It is designed to advance characterization of the exposure information that is required to translate findings from computational toxicology into information that can be directly used to support risk assessment for decision-making and improved public health.

The Tox21 Program mentioned previously was reviewed in greater detail during this session. This Program combines expertise across three federal agencies in a number of research areas, including experimental toxicology, high and mid-level throughput screening systems, lower organism modeling, *in vitro* and genetic modeling, and computational toxicology and validation. Tox21 activities include integrating new rodent and human *in vitro* data with historical rodent *in vivo* data from NTP and U.S. EPA, as well as human *in vivo* data from drug trial studies from the U.S. Food and Drug Administration (FDA). Researchers are now using quantitative HTS (qHTS) to extend beyond the capabilities of conventional HTS. Compounds are tested at 15 different concentrations (as opposed to a single concentration with conventional HTS) to obtain concentration-response curves and robust activity profiles for each compound. This approach has a throughput capacity of more than 200,000 concentration-response profiles per week. Electronic counter-screens are then used across more than 200 assays to integrate results and to identify key toxicity pathways. The qHTS system allows users to rapidly access biological profiles of chemical series, and review interactive heatmaps that provide details of the assay results. Tox21 assays screened at NCGC to date include cell viability, enzyme pathways, DNA (deoxyribonucleic acid) damage, nuclear receptors, and assays measuring inter-individual variation in chemical response in cell samples from identical twins.

Approaches for identifying key toxicity pathways include evaluation of a wide array of toxicogenomic data, genetic associations with human disease, the existing pathways universe, as well as resources available from reagent companies and contract research organizations with a goal of developing a comprehensive toxicity pathway map. Current limitations to the HTS approach include the fact that not all types of *in vitro* assays are compatible with HTS and that not all substances can be tested *in vitro*. In addition, responses are limited to cell-autonomous effects of parent compounds and *in vitro* assays lack numerous factors present in *in vivo* systems that can influence compound uptake and metabolism. To address these limitations, appropriate cell types will need to be identified, more complete pathway and phenotypic assays will need to be developed, metabolism and genetic heterogeneity will need to be incorporated, and existing data will need to be collated more completely. In addition, meta-analysis informatics will need to be developed to enable use of data by others, and validation of testing strategies and incorporation into regulatory decision-making will need to occur. These and other challenges highlighted in the first data analysis summit of the ToxCast™ program in May 2009. These challenges will continue to provide opportunities to improve the methods and technologies needed to enable prediction of human toxicity and disease from *in vitro*, *in vivo*, and *in silico* data.

Research on gene-environment interactions is increasing our understanding of the relationship between genetic and environmental factors and disease endpoints. Risks to individuals from exposure to environmental factors can now be identified according to genetic variants. Technological advances will soon allow comprehensive recording of genetic variance across populations. The National Institutes of Health's (NIH) Genes, Environment, and Health Initiative (GEI; NIH, 2009) aims to better understand the linkages among genetic susceptibility, exposure, and disease. This is accomplished through modeling of multiple exposure pathways to determine thresholds of dose and dose rates associated with chronic toxicity and with the development of disease. Experimental genetic models can play an important role in improving our knowledge base regarding gene-environment interactions and identifying the multi-gene basis for disease that is otherwise difficult to replicate in human populations. Primary aims of the GEI are to: (1) predict potential population-level ranges of biological response to aid cross-species extrapolation and risk characterization; (2) identify and characterize allelic variants of genes that are associated with individual differences in response to toxicant exposure; and (3) identify the genetic basis and MOA for toxicity and disease in animal models and correlate these with human disease genes to aid extrapolation and prediction between species.

The topics of communication of science information and of the reporting of risk were presented from a journalist's perspective. An initial point was that the majority of reporters and editors do not intentionally misrepresent risks because they want to boost profits, but rather because the information that grabs readers also grabs reporters. Science reporters and other journalists also face particular pressures that can influence how risk is reported in the media. These include 24/7 news cycles, the challenges of weighing scientific information from diverse sources, understanding the technicalities of the scientific results, and the need to balance the responsibility of raising awareness with the responsibility of not alarming the general public unnecessarily. Novelty, originality, proximity, personality, worry, controversy, conflict, and their relevance to real life and to a diverse audience are the qualities that make news. In a science-centered age where the public demand for professional and impartial analysis is increasing, the profession of science journalism is trending downwards. Meanwhile, online blogs increasingly hold significant sway in public opinion, often without a proper balance of different viewpoints or sufficient credible evidence. Factors that facilitate media hype and errors need to be recognized and addressed. In addition, scientists and researchers should resist the temptation to describe their studies using inflated metaphors and terminology, such as 'groundbreaking,' and remain true to the significance of their studies. Several solutions to the problem were suggested, including more training in the basic sciences for journalism students and increased investment in schools of journalism. News organizations should also provide journalists a science policy beat so that they can improve their reporting of public issues that span both science and policy. Looking to the future, new models of journalism are needed to fill gaps where for-profit journalism is now failing.

### 3.0 Breakout Sessions

The three breakout sessions were designed to provide forums for interactions and discussions among the participants on each of the workshop themes. Participants had the option to attend any of the three breakout sessions, which were run in parallel. In brief, the key questions for the three sessions were:

- Advanced technologies – How can the data from the new technologies and high-throughput assays for genes, proteins, and metabolism be effectively interpreted for risk assessments of chemicals?
- Exposure – What innovations in exposure science are needed to better characterize biologically relevant exposures to chemicals and to understand their implications for human health risks?
- Communication – Which frameworks can best communicate new scientific information and research outcomes to all stakeholders throughout the research and decision-making processes?

A cross-cutting theme for all of the breakout sessions was increased understanding of genetic influences and gene-environmental interactions regarding chemical exposures with a focus on improved risk assessments for susceptible populations, including children.

#### 3.1 Session 1: Advanced Technologies

This session focused on approaches to effectively interpret the large volume of data now emerging from the new biological technologies. Generation of data using the ‘omic’ technologies, which include genomics, proteomics, metabolomics, and transcriptomics, is an increasing part of everyday research activities in laboratories around the world. However, these cutting edge research efforts have not been matched with development of approaches to interpret the data in ways that can inform risk assessment and address questions about the potential adverse human health effects from exposures to chemicals.

This session explored interpretation of genomics data, particularly through bioinformatics, using a context of systems toxicology and mechanism-based risk assessment. An objective of this session was to evaluate how data from other fields, such as epidemiology and genetics, can facilitate interpretation of ‘omics’ data. It also included a look ahead towards upcoming ‘omics’-based technologies and the challenges and opportunities they will present concerning analysis and interpretation of the data.



Christopher Austin, National Institutes of Health Chemical Genomics Center, USA

## *Effective Interpretation Data from the New ‘Omics’*

Presentations on the first day focused on effective interpretation of new ‘omics’ tools for characterizing dose-response and for understanding MOA for chemical hazards. Genomics provides the means not only to evaluate transcriptional changes across the entire genome but also to focus on the changes in individual genes and pathways. In the area of dose-response, microarray analysis of gene expression can provide insights into the cellular processes affected by different doses as well as the underlying biology of dose-dependent transitions. Current challenges for the ‘omics’ data include how to integrate heterogeneous types of information and knowledge sets across different disciplines and ultimately, how to use such information for risk assessment. The data generated need relevant phenotypic anchors for proper interpretation, but in many cases, these do not yet exist. In response to these challenges, several organizations are developing approaches for the effective interpretation of data from the advanced technologies.

The topic of the first presentation was interpreting genomic data to understand mechanism and the value of using network approaches to address this question. Networks are important because they, not genes, drive biological processes. All levels of biological information have dynamic systems associated with them, and all systems interact in different ways to form networks. Because correlations in gene expression can be considered the result of network interactions, they can serve as a basis for understanding causal relationships in biological systems. Bayesian networks are an approach that can provide a map, based on data, of which genes influence others; data from microarrays and other gene expression analyses can be used to identify such networks. These Bayesian networks also can be used as a predictive, testable model that can be validated as well as refined through controlled perturbations. Because Bayesian networks can be linked back to known biological pathways, they can suggest mechanistic links. These predictive models for system responses can serve a wide range of useful applications, but basic biology will retain an important role during the development of network approaches to understand ‘omics’ data.



Timothy Gant, University of Leicester, UK

The second presentation described another approach for effective interpretation of ‘omics’ data. Applying genomic tools to dose-response studies allows for a broad survey of the transcriptional responses in different genes and the alterations that result from changes in dose. The presenter described an experimental approach for using transcriptomics to predict hazard and dose-response behavior for chemical carcinogens. Benchmark Dose analysis was also used to analyze the data, allowing reference doses to be estimated for individual genes and functional categories. Their results indicated that short-term transcriptomic data can predict long-term toxicological hazard and that functional analysis of predictive signatures can identify key pathways involved in adverse responses. An important new finding was that the investigators determined that transcriptomic dose-response alterations correlated with tumor incidence. They also reported that pathway-based transcriptomic dose-response data can provide insights into the

MOA as well as provide reasonable reference doses or point of departures for performing cancer and non-cancer risk assessments.

The next presentation described the 6th European Union Framework Programme for Research and Technological Development (FP6), an integrated project on predictive toxicology called PredTox. This project involves development of an integrated database populated with comprehensive data from *in vivo* experiments of 14 compounds that previously failed during drug development, and from two extensively characterized model compounds (Genedata, 2009). The PredTox consortium involves 20 partners, including pharmaceutical companies, academic institutions, and small- and mid-size enterprises. The objective of this project is to enable policymakers to make more informed decisions when evaluating the safety of chemicals by combining results from ‘omics’ technologies with conventional toxicological endpoints. PredTox partners have benefited from the sharing of expertise, methods, and costs, and from closer cooperation between industry and academia. By analyzing and data mining the information contained in the database, the potential exists to predict toxicities of various compounds and to identify mechanisms of toxicity. The technical and operational feasibility of the approach has been demonstrated. Benefits of systematic measurement of conventional and ‘omics’ data and coordinated analysis across domains include increased mechanistic understanding and higher qualifications for new biomarker candidates.



Martin Stephens, Human Society of the United States, USA

The following presenter discussed connectivity mapping for recognition of early toxicity using the FP6 PredTox data. A connectivity map is a collection of gene expression profiles and related tools that can be used, by comparison to a test signature and to reveal connections among compounds, genes, and diseases based on gene expression similarities. Use of this approach is based on the assumption that a biological state, whether physiological, pathological, or induced by chemical or genomic perturbations, can be described in terms of a genomic signature. Using this approach, a genomic signature is compared to a selection of reference profiles to determine whether a positive or negative connection exists. Connectivity mapping shows great potential for developing new biological hypotheses through leads from potentially unexpected connections and serving as a high-throughput screening process for chemical toxicity testing. Other potential applications include identifying novel toxicological properties of candidate compounds and chemicals, being extensible to other ‘omics’ technologies and advancing replacement of animal models by developing *in vitro* profiles.

A fifth presentation described efforts to interpret genomic data by identifying functional modules. By using functional modules of genes instead of studying individual genes at a single point in time, it is possible to develop more stable and representative gene markers. Another benefit is that functional modules focus more on the specific genes than pathways. Functional modules also overcome artificial, annotation-based pathway boundaries that can be subjective based on the user. Furthermore, functional modules may be used as mechanistic models of

compound actions and as a complement to statistical approaches. At the Max Planck Institute for Molecular Genetics, researchers have developed a database, the ConsensusPathDB (Max Planck Institute, 2009), for integrating human molecular interactions to produce a more comprehensive picture of cellular interactions. Source data for the database is derived from publicly available databases as well as manually fed data, and algorithms incorporated within the database prevent redundancies in interactions from the various source databases. Development of functional modules is an iterative process that involves mining the genomics data to produce candidate genes, performing a meta-analysis to identify robust markers across different experiments, and then identifying interactions that connect the selected gene markers. Analyzing these interaction networks is necessary for understanding biological processes and how changes in these processes can result in human disease.

### ***New Descriptors of Adverse Effects***

Presentations on the second day highlighted additional new approaches for evaluating the effects of chemicals, including micro ribonucleic acids (miRNAs), epigenetic status, and the influence of genetic background as evidenced by single nucleotide polymorphisms (SNPs).

The first presentation during this session discussed miRNAs as markers and modulators of toxicity. miRNAs are small non-coding genetic species that are located in regions between gene sequences. They are under the control of promoters with the potential to be induced by chemicals and can also interact with messenger RNA to regulate gene expression. Initially, miRNAs could be viewed as adding complexity to the data generated because they represent yet another category of RNA for consideration. However, two positive points are that the numbers of miRNA sequences are fewer than the numbers of genes, with estimates varying between 500 and 2,000 depending on species, and that the data on their differential expression are easy and inexpensive to generate. In addition, miRNAs show great promise as markers and modulators of toxicity; because they can be expressed specifically by a target organ and can also be detected in plasma, they could serve as biomarkers distal to a site of injury. Because they are potentially organ-specific, they may have a role in hazard identification for specific toxicities. In addition, because miRNAs can regulate the translation of other genes involved in toxic responses, they have a likely role in toxicity mechanisms. Finally, because some miRNAs are known to be polymorphic and polymorphisms can be associated with diseases, miRNAs may be a factor in determining susceptibility; more research is needed to fully establish this link.

A second presentation explored inter-individual differences in toxicity responses using *in vitro* and *in vivo* approaches. Inter-individual variability can be observed either at the genetic level or at the population level; it is also a regulatory concern because many mechanism-based investigations have been unsuccessful in identifying susceptible individuals. The small size of human populations that are susceptible to adverse effects associated with chemical exposures can limit the statistical significance of studies conducted only in humans. Hazard characterization using animal models that have homogeneous genetic backgrounds presents limitations for use in human health risk assessments because humans have heterogeneous genetic backgrounds. To address this concern, gene sequencing studies have been conducted and they demonstrate that mice are more genetically diverse than humans and possess more SNPs. Therefore, a diverse

mouse population could be used as a model to understand and predict adverse toxicity in heterogeneous human populations through guided resequencing (Harrill et al. 2009).

Continuing on the topic of variability among human populations, the next presentation reviewed the topics of susceptible populations, life stages, and critical windows of exposure and their relevance to chemical exposures. Specifically, the presenter discussed genetic polymorphisms and presented examples where they can affect pharmacokinetics or health outcomes. Genetic polymorphisms have the potential to alter the metabolism of chemicals by modifying chemical clearance, detoxification, and the formation of active metabolites. In addition, genetic polymorphisms can alter cellular defense mechanisms and toxicodynamics. While studies have demonstrated the potential of genetic polymorphisms to affect health outcomes, in general, risk assessments have not used this information to characterize population variability or to adjust risks for susceptible subgroups. Major data needs still exist. For example, while polymorphisms in metabolism genes have the potential to alter activity and internal dose, researchers still need to determine the specific isozymes involved in chemical metabolism and to further examine the influence of polymorphisms on metabolism. To fully explore the implications of genetic polymorphisms on risk, validated physiologically-based pharmacokinetic (PBPK) models are needed to simulate the fate of environmental toxicants in susceptible populations.

To close this session's presentations, the final presenter provided an overview of the existing 'omics' technologies, including the promises, successes and setbacks, and current use of these technologies to work at the FDA. Topics discussed included safe drug development and strategies for development of biomarkers as indicators of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention. The presenter noted that, although 'omics' technologies offer tremendous potential, evolution of these technologies is still needed, particularly in proteomics. Furthermore, data standards are needed to assess the data quality, particularly for metabolomics and proteomics. Some standards are now available for pharmacogenomics, but more are needed. The eventual development of these standards will provide uniform analytical capabilities. While the costs for generating the data are decreasing, the costs of interpreting the data are increasing. Tools to analyze and interpret the 'omics' data will come, but they will take time.

### ***Panel Discussion***

To conclude the second day's session, participants reviewed the information presented during the advanced technologies session using the questions in Figure 2 as starting points for their discussions.

**Figure 2**  
**Questions for the Advanced Technologies Breakout Session**

***Adaptive versus Adverse Responses in Pathways***

1. Most biological pathways have an inherent level of robustness that allows for some perturbation without adverse effect, i.e. adaptation. In this context:
  - a. Can adaptation be regarded as normal and reversible without consequence?
  - b. What experimental approaches in conjunction with new technologies could be used to identify the thresholds of transition from adaptive adverse level at either gene expression, protein, or metabolite level?
  - c. What bioinformatic and statistical tools still need to be developed to analyze omics data with respect to definition of such thresholds?
  - d. How many genes or proteins need to be altered in a pathway in order to call it perturbed?
  - e. When analyzing transcriptomic data, is the traditional “enrichment analyses” a reasonable criteria for evaluating whether a pathway is perturbed, or can a pathway be perturbed that is not “enriched”?
  - f. What does the direction and the amplitude of change in transcript levels tell us regarding the biochemical processes underlying an adverse effect? Is pathway analysis the most effective bioinformatics method to analyzing and interpreting data across the ‘omic platforms’?
  - g. Should more weight be given to the rate limiting (control point) genes in a pathway when undertaking a pathway analysis?

***Genetic Variability and Susceptibility***

2. In the context of the White et al. (2009) article,
  - a. How can the new technologies and data analysis approaches be used to directly examine the influence of population variability and susceptibility on the shape of the dose-response curve in the low dose region?
  - b. How can population and individual genome data be incorporated into a risk assessment? Does it need to be incorporated? What is the frequency limit for considering the impact of a polymorphism in a risk assessment?
  - c. How important is epigenetic change likely to be when considering genome alteration giving rise to differential sensitivity?
  - d. New sequencing methods are rapidly adding to the knowledge base of polymorphisms and epigenetic modification. Is it feasible to incorporate all these data into a risk assessment?

Adaptive versus Adverse Responses in Pathways

Regarding the questions on adaptive versus adverse responses in pathways, participants emphasized that development of appropriate interpretive tools for the data will continue to be a critical element for advancement of the ‘omics’ field. Participants also noted that because most environmental exposures are at levels much below those of pharmaceutical compounds, generation of low-dose data remains a high priority. The need for low-dose data was also highlighted in the NRC report recommendations for risk assessment (NRC 2008). Once the data are generated, it will be important to be ready to interpret results in ways that can distinguish adaptive and adverse responses. Discussants noted that phenotypic anchoring is also important, yet questioned whether in making new linkages, anything new will be learned. Other challenges discussed include balancing the number of doses and interpretation of dose-response for each gene. It was noted that a procedure for moving from gene-based dose-response to pathway-based dose-response under development. The significance of biological pathways will also need to be

tested. Questions were also raised about the determinism of the pathways and whether or not linear dose-response approaches will be applicable. For larger scales, such as population-based studies on outcomes from dietary improvements, these methods will provide opportunities to look at whole populations when interpreting adaptive versus adverse responses.

### Genetic Variability and Susceptibility

On the topic of genetic variability and susceptibility, the group addressed questions concerning how individual polymorphisms might realistically be incorporated into risk assessment and risk management. By providing more information on the range of potential outcomes, new technologies will assist in drawing lines for public health protection and improved decision-making. In a risk-averse society, outliers are likely to gain attention, so questions remain on how to manage information and communications on rare polymorphisms. New tools will allow for opportunities to estimate the diversity of populations better than before and to test which chemicals will be highly variable, aiding priority setting. The question of what is an adverse effect remains central and still unresolved. Likewise, answering the key questions that are important for risk assessment, and how new and advanced technologies can best contribute to improved risk assessment, remains a central challenge. It will remain important to focus not only on pathway perturbations but disease outcomes. As in many areas, there are challenges in translating dose response data from highly defined experimental systems to the general population. Genomics will not necessarily provide different results than those from long-term animal studies, but it will be a faster, more efficient way of getting those results. In addition, time course genomics provide MOA information and go beyond what is gained from animal studies and help identify risk specific doses that lead to disease outcomes. Improvements are needed in how numbers are communicated to the public. As an example, percentages do not communicate as well as absolute numbers (e.g., “three-fold increase in risk” is difficult to understand while “one in one million” is easier). Communication and education will remain important for interpreting complex scientific findings for lay or public audiences.

### **3.2 Session 2: Exposure Science**

This session focused on innovative approaches for characterizing biologically relevant exposures and determining their implications for human health risks. As noted previously, understanding genetic influences and gene-environment interactions as essential elements for improving risk assessments for susceptible populations was a cross-cutting theme. Interpretation of biomonitoring data was also considered an important element for characterizing exposure. Participants were asked to consider the following points during the presentations and discussions:

- The need to focus exposure and epidemiology studies on measurement of exposure information that is relevant for understanding health endpoints
- The need to inform design of health studies (epidemiology and toxicology)



Marsha Morgan, U.S. EPA, USA, and Fumiaki Shono, JCIA, Japan

- Characterization of sensitivity and susceptibility
- Linkages between environmental exposures, susceptibility due to genetic variation (polymorphism), and toxic response
- Computational approaches for integration and interpretation of exposure and dose-response data
- Analysis approaches for evaluating multidimensional data
- Simulation tools for modeling exposures across the different levels of biological organization that would support design and interpretation on toxicity testing data

The speaker presentations and the discussions in this breakout session were categorized into four major themes that are discussed below.

### *Approaches for Measuring and Understanding Exposure*

Cumulative and integrated approaches are becoming the new norm for exposure and risk assessments. Such a focus underscores the need for a trans-disciplinary approach to exposure assessment and the importance of assembling multi-disciplinary teams to conduct the research.

The first presentation outlined two models that have been used to study human exposures to compounds and pollutants both on individual and global scales. The first, USEtox™, was developed as a result of four-year collaboration between the United National Environment Programme and the Society of Environmental Toxicology and Chemistry. This model takes into account exposures to compounds from agricultural soil, natural soil, freshwater, coastal marine water, and air on both continental and global scales. A characterization factor for each of these sources is calculated based on the intake fraction, the intake of a pollutant over the amount of pollutant released into the environment, and the ED<sub>50</sub> value, which is the dose that produces a response in 50% of the test population. The model has been applied to more than 2,000 substances in the human toxicology and ecotoxicology fields. The second model, IMPACT, is a spatially resolved model that evaluates the effect of global factors such as rainfall rate, wind, animal production, population density, location of emission, agricultural intensity, and urban versus rural emissions on regional exposures. The multi-scale aspect of the model allows researchers to evaluate exposures with a high level of resolution at point sources and in areas with high population densities.

The next presentation focused on statistical approaches to improve exposure measurements. The basic premise was that good characterization of dose-response does not require that everyone be measured perfectly or that every available measurement instrument be used on every subject (Morara et al., 2007). Careful statistical analysis can be used to combine results from a detailed exposure assessment for a subsample of a population under study with results from the entire cohort using a less accurate, but less expensive and more practical assessment. A key factor for this approach is that the less accurate assessment must correlate well with the detailed exposure assessment. An example described for this approach was taken from the NIH National Children's Study (NCS) on exposure to chlorpyrifos and the onset of autism; a full assessment was completed on 3,000 children while a simple dietary assessment was completed on the complete cohort of 100,000 children. Results indicated that this statistical model was able to accurately determine exposure levels for the entire cohort. A key message

from the presenter was that exhaustive exposure measurements, that is, measuring everyone perfectly, are not necessary to get useful information. However, studies must be designed to account for the biological/exposure basis for the measurements so that meaningful interpretation of the data can be applied to risk assessment purposes.

### ***Use of Pharmacokinetic Models to Advance Exposure Science***

Several speakers discussed approaches that use PBPK models to better understand human biomonitoring data and high-throughput testing data.

The first presentation described a framework for risk assessment of environmental chemicals in humans using a forward dosimetry approach. Investigators have been able to estimate chemical concentrations in the human body from doses in animal studies using *in vitro-in vivo* extrapolation and information on inter-species differences. For instance, exposure to tobacco smoke can be estimated by monitoring cotinine in rats and humans and applying a simplified nicotine/cotinine PBPK model. Similarities have been found between simulated and measured concentrations of selected parent compounds and their primary metabolites in humans using this model.

To better understand the potential adverse effects of bisphenol A (BPA), researchers have been working to link urine biomarkers for BPA to exposure and its effects through computational PBPK approaches. Both rodent toxicology and human exposure data for BPA are available, but the human and rodent tissue doses have not been compared systematically. The conventional method of BPA exposure assessment is to back calculate exposure from urine biomonitoring concentrations, where the urine concentration is multiplied by the assumed daily urine volume and normalized to creatinine concentration multiplied by the assumed creatinine elimination rate. This new human PBPK model for reverse dosimetry improves the basis for urine biomonitoring by eliminating the assumptions. This study employs known physiological parameters and experimental conditions and uses distributions for missing parameters. Ultimately, this method could be employed for dose extrapolation for ToxCast™ data.

Another presentation outlined a new approach for evaluating ToxCast™ data that employs biomonitoring data and PBPK methodologies. Investigators compiled data on physiologically relevant concentrations, such as serum or plasma concentrations from animal studies, for four selected chemicals and compared the responding ToxCast™ assay data for these chemicals to those concentrations. Initial results indicated that the concentration distribution is quite wide, but generally corresponds to physiologically relevant concentrations. It is important, however, to take into account the *in vitro* cell culture system conditions and media used in relation to the actual physiological environment (e.g., the time course of an *in vitro* experiment compared to chronic *in vivo* responses). The speaker noted that for screening and prioritization of a chemical of potential interest, exposure should be viewed as the first and most important screening criterion, and not just a useful adjunct to toxicity testing.

An integrated *in vitro* and computational approach to relate exposure, dose, and toxicity to HTS data was also presented. The method under development involves correlating the half-maximal effective concentration (EC<sub>50</sub>) values generated in HTS to human dosimetry and exposure. Investigators have used *in vitro* assays for hepatocyte clearance and plasma protein binding to provide critical pharmacokinetic information on a subset of ToxCast™ chemicals. Integration of these *in vitro* assays with computational modeling allows estimation of the oral exposures required to produce steady state *in vivo* concentrations equivalent to EC<sub>50</sub> values in high-throughput assays. Further comparisons of equivalent oral exposures to human reference dose values will allow researchers to estimate the margins of exposure and provide additional context for chemical prioritization. Remaining challenges include interpreting the relevance of *in vitro* assay results to *in vivo* endpoints, cross-species differences in assay design and pharmacokinetics, and, ultimately, how these data will correlate with human health and exposure.



S. M. Rappaport, University of California – Berkeley, USA

### ***Exposure Studies in Populations***

Several presentations focused on results from studies in populations concerning exposures to specific chemicals or sets of chemicals.

The U.S. EPA's Mechanistic Indicators of Childhood Asthma (MICA) research program includes studies on genomic markers of exposure, susceptibility, and effects that can be used for gene expression analysis to identify different types of asthma, termed endotypes. The research has identified several components that underlie asthma endotypes and that are consistent with previously proposed classifications. These endotypes can be used to better define susceptible subpopulations for risk assessment concerning air pollutants. MICA data can further be employed to define mechanisms for these endotypes. For example, U.S. EPA data suggests that asthma cases linked with metabolic syndrome are potentially mediated by innate immune responses through priming or activation signals for adipose. This information can be further interpreted to establish human bioindicators in blood. In the case of metabolic syndrome links, monitoring the “activation state” of circulating monocytes and neutrophils may serve as a good bioindicator for obesity-related asthma. The presentation closed by describing how a systems-based modeling approach that envisions linkage of data among three levels of molecular, key event, and population networks to improve understanding of human disease, such as asthma.

The topic for another presentation targeted exposure research designed to improve decision-making and included a review of an initiative to better understand mechanisms that can lead to development of breast cancer. The speaker described how mechanistic information can help identify chemicals for screening, facilitate risk management and exposure reduction, and

support new exposure measures for epidemiological studies. In a recent household exposure study, the speaker described measured levels of suspected endocrine disruptors in homes on Cape Cod, Massachusetts and in Richmond, California (Rudel et al., 2003). The study reported detection of an average of two dozen endocrine disruptors in each home, the presence of the insecticide dichlorodiphenyltrichloroethane (DDT) in two-thirds of the homes, and measurements of chemical concentrations above guideline levels in all homes. The study indicated that elevated concentrations of polychlorinated biphenyls (PCBs) in the air of some of the homes as well as in blood samples from the residents that may be attributable to a floor finish not previously identified as a PCB source. In addition, elevated levels of polybrominated diphenyl ether (PBDE) detected in household dust concentrations in California were attributed to the use of PBDE finishes currently required by that State's furniture flammability standards. Based on the results, the speaker emphasized that understanding both biological mechanisms and human exposure data must form the basis for human health risk assessment.

Prenatal exposure to arsenic was described as model approach that combined genomics, computational biology, and systems-level analysis used to understand responses to environmental exposures. Investigators studied a population in the Ron Pibul District of Thailand where arsenic levels are very high due to tin-mining activity from the 1950s through the 1980s (Fry et al., 2007). Blood from newborns whose mothers were exposed to varying levels of arsenic as measured by toenail concentration were used for expression profiling. Researchers developed a two-class prediction algorithm to determine whether gene expression signatures from a training population of newborns could be used to classify arsenic exposure in a larger test population. The training population was used to identify expression patterns that distinguish between exposed and unexposed subjects. These results were then translated into an arsenic-associated gene set that was used to classify the maternal exposures among the other newborns with relative accuracy. In later work, the investigators were able to narrow down the gene set yet retain equally predictive capabilities. They also studied molecular interactions among the gene biomarkers to better understand the biological pathways modulated after exposure to arsenic.

### ***Overviews of Current Exposure Programs***

Two presentations described ongoing research programs at federal agencies and academic institutions in the US with a focus on advancing exposure science.

The National Exposure Research Laboratory (NERL) at the U.S. EPA conducts human health and ecological exposure research that provides pertinent databases, predictive models, and analytical tools needed by the agency to fulfill its mission. The research is directed towards improvements in the ability to characterize, predict, reconstruct, and manage exposures to tens of thousands of chemical contaminants, a wide range of biological stressors, and many physical and sociodemographic stressors with special consideration for susceptible and vulnerable populations. NERL is particularly focused on the methods, such as data collection, analytical chemistry, computational/bioinformatics, as well as empirical, deterministic, mechanistic, probabilistic models that drive exposure assessments. Other areas of research include interpretation and use of biomarkers, systems biology approaches to environmental linkages, exposure reconstruction, metabolomics in exposure, and community cumulative risk. NERL

recognizes that exposure science will play a critical role in development of new risk-based frameworks in parallel with current activities to advance toxicity testing in the 21<sup>st</sup> century.

The Environmental Bioinformatics and Computational Toxicology Center (ebCTC) is a collaboration among the Robert Wood Johnson Medical School, Rutgers University, Princeton University, and the FDA. The objectives of ebCTC are (1) to address the toxicant source-to-outcome continuum through development of an integrated, modular, computational framework; (2) to develop predictive cheminformatics tools for hazard identification and toxicant characterization; and (3) to demonstrate these tools through applications in quantitative risk assessment. Investigators use a multi-disciplinary (computational, engineering, and systems) perspective to develop new frameworks and tools to build on past developments. The speaker outlined three case studies that are representative of ongoing work being done at ebCTC: (1) an investigation of dibutyl phthalate (DBP) exposure using toxicogenomic studies; (2) a study on the liver toxicity of conazoles; and (3) an investigation of conazole-pregnane X receptor (PXR) interactions at the PXR antagonist binding site.



William Welsh, University of Medicine & Dentistry of New Jersey, USA

### ***Panel Discussion***

In the last part of the breakout session, participants were asked to identify significant research questions and gaps for advancing exposure science and for developing biologically relevant exposure to inform toxicity testing (Figure 3).

<p><b>Figure 3</b></p> <p><b>Topic for the Exposure Science Breakout Session</b></p> <p>Identify what you see as significant research questions and gaps for advancing exposure science and for developing biologically relevant exposure to inform toxicity testing</p>
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To begin this part of the session, three panel members presented several ideas designed to initiate the discussions. The first panel member reviewed the need to focus on cumulative risk caused by multiple stressors and multiple sources; to develop people-oriented models; and to introduce a tiered screening approach. The second panelist stressed that many pathways link source to health outcomes and that all must be considered. He also emphasized that the question of risk can be answered through epidemiology and the question of how can be addressed in the field of toxicology, but the questions of who, where, when, how much, and what can we do must all be answered by the field of exposure science. The last panelist tasked the group with developing an improved definition of exposure that includes source-to-dose modeling as well as

upstream effects, decision-making in addition to assessment, and focusing on exposure science as trans-disciplinary science.

The presentations and resulting discussions illustrated a number of recent advances in tools to help characterize biologically relevant exposures and their implications for human health risks. New tools have been developed (1) to understand and evaluate the source-pathway-receptor-dose-effect continuum; (2) to help optimize data collection through statistical means; (3) to measure genetic biomarkers of exposure; and (4) to interpret biomonitoring data and high-throughput data through PBPK modeling.

Participants commented that exposure assessment has lagged behind toxicity testing for some time, but that the focus has begun to shift towards approaches in which biologically relevant exposure data can complement, and even outweigh, toxicity data for evaluating real-world risks to chemicals. Success in this area depends on making exposure assessment a trans-disciplinary effort. Exposure assessments are multi-functional, and a multi-disciplinary team is necessary to address issues such as environmental contaminants, chemical mixtures, indoor air exposure, and the risk of multi-use consumer products. If the science continues to advance along these lines, real-world exposure evaluations will become a necessary tool in effectively determining which toxicological studies are performed.

### **3.3 Session 3: Communication**

This session focused on the key role that communication will need to play to foster understanding about the innovations in biological, exposure, and risk sciences. This understanding is essential to build trust among the public and involved stakeholders regarding the value and potential use of this new information for decision-making about risks from exposures to chemicals. Interpreting and translating the emerging data into meaningful information, however, is a current challenge. For example, biomonitoring studies continue to provide information about human exposures to chemicals at rates faster than our ability to interpret and translate the results in a context that is relevant to individual and public health concerns. Progress in our abilities to interpret and communicate the emerging new information must parallel the technological advances.

In brief, communication can be defined as the science of processing information. The social sciences can provide tools to meet difficult communication challenges and to improve our understanding about different audiences and their educational and decision-making processes. This session explored the methods, challenges, and ethical considerations for engaging and communicating with stakeholders. Topics included how best to provide stakeholders with information to develop informed personal or societal decisions and how risk perception can vary with trust level and prior personal experience.

#### ***Communication Approaches***

Two presentations about communication of scientific information described the National Health and Nutrition Examinations Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC) and the NCS conducted by a consortium of U.S. federal agencies.

The CDC was described as the steward of its extensive NHANES data set that includes information from personal interviews, standardized physical examinations, laboratory tests, and biomonitoring results from an annual sample of 5,000 study subjects in the United States. Findings from this survey are used to determine the prevalence of major diseases and risk factors for diseases and to assess nutritional status and its association with health promotion and disease prevention. Data from this survey are used in epidemiological studies and health sciences research to help develop sound public health policy. Because the CDC has conducted this study for 50 years, it can serve as a model for other studies, such as NCS.

The NCS is a longitudinal study of environmental influences on children's health, growth, and development for which environment has been broadly defined to include chemical, physical, biological, and social factors. The study has been designed with the statistical power to examine common environmental exposures with less common outcomes and multiple exposures with common health outcomes. The study began in 2009 and will include health and personal questionnaires, biomonitoring samples, environmental samples, and physical examinations of mothers, fathers, and children.

The presentations about these government-funded studies described the necessity to provide data in a timely but controlled way to the study participants, the public, and the research community while also protecting study subject confidentiality. Concerning confidentiality issues, the CDC allows controlled access to confidential or sensitive data in ways that protect privacy, such as special use agreements and restricted access through a data center. It will release data only after careful planning and evaluation to ensure no mistakes are made. CDC requires that NHANES statistics be “of high quality, timely, comprehensive, as well as specific, standardized, and adequately analyzed and indexed,” and that CDC “shall publish, make available, and disseminate such statistics on as wide a basis as is practicable” (Public Health Service Act Section 306, 1956). However, U.S. public law also protects data confidentiality—Public Health Service Act 308(d), the Privacy Act, and the Confidential Information Protection and Statistical Efficiency Act. Similarly, the NCS must answer promptly questions put forth in the Children's Health Act, access by researchers must be granted, but protection of confidentiality and data integrity are also vital. In both programs, the managers must balance efforts to collect data and efforts to allow timely access to the data. Information access issues tend to be more complex and often require more staff and more costs than anticipated due to many study participants who want information and numerous researchers who want to access and analyze the data.



Kathryn O'Hara, Carleton University, Canada

It was noted by the speakers that communication protocols must be developed for each biomonitoring study and included in the consent process, prior to participant recruitment. The protocols should indicate how the data would be protected and when and how test findings will be communicated. This can be difficult because some of the tests are not known at the time of collection, tests results are completed at different rates, and there is variability in the implications of the results, which can also change over time. One speaker suggested that the protocols should also indicate how participants can use results to take action, and provide information to help

interpret individual results, such as providing available regulatory benchmarks and distributing information.

The CDC develops an access plan early in the study design process, and it is an integral part of the study design. The access plan includes principles governing access to the data and how confidentiality will be protected, when and how data will be released or made available in a controlled way for analysis, and the practices or mechanisms by which the policies are implemented. Complex studies require complex access plans.

Reporting back results to participants must also be carefully planned and evaluated. The NHANES examination consent process includes the list of health measurements that will be reported and how (e.g. by phone or e-mail). If a medical concern is suspected at the time of examination, the participant is advised to go to their health care provider. Results can be reported back to participants if certain criteria are met as judged by a Physician Advisory Group. The report back communicates what the finding is and what the person could do about it. It is standardized to the extent possible. The NCS program will rely on an independent Study Monitoring and Oversight Committee to review test results over time and determine how and when additional results should be reported to the participant. This committee's responsibilities are acknowledged in the consent process.

Participants in NHANES are also informed that they will not be contacted with results from future studies on stored specimens because they are currently limited to studies that do not yield clinically relevant findings. The program is evaluating how to broaden research on stored specimens to include clinically relevant tests and how to report back to participants. A certain level of participant communication is required—they need to notify the program of a new address when they move and it is up to them to go to the Web site to find out what new tests are being conducted on stored samples.

Speakers also noted the importance of addressing communication needs for different cultural contexts and literacy. For example, NCS is piloting a method of video consent to supplement written consent. Studies must be willing to refine communication approaches based on interim feedback and balance between right-to-know and capacity to act. For instance, reducing exposures to legacy pollutants such as DDT may not be realistic. The NCS representative also noted a major challenge associated with biomonitoring studies that involve children. There is a transition from the stage where the parents consent on behalf of the child participant to a stage when the child participant reaches the age of consent and may have different values. One speaker shared that Altman et al. (2008) reported that nearly all participants in a set of studies requested individual results regardless of the uncertainty. Reasons included curiosity, a desire to advance science, an interest in understanding exposure routes and sources, and information to take action.

The consensus conference was presented as an approach that can be used to educate the general public and stakeholders about issues surrounding scientifically complex and controversial topics. The approach gathers input from informed lay people in a facilitated meeting series format. The Danish Board of Technology uses consensus conferences to provide input to its Parliament. It is also a European Citizen's Deliberation method, called Participatory

Technology Assessment, which has been used in nine European countries. Other countries, including Argentina, Australia, Belgium, Canada, Israel, Japan, New Zealand, and South Korea have held consensus conferences.

As an example of this approach, two presenters described the Boston Consensus Conference on Biomonitoring and session participants had the opportunity to view a video describing the process and its outcomes (see [www.biomonitoring06.org](http://www.biomonitoring06.org)). The goal of this project was to educate the general public and stakeholders about biomonitoring and the related ethical, legal, social and scientific issues. It was noted that the recruitment process screened out persons with strong existing opinions and those who had a vested interest in the outcome. Facilitation and education materials were critical to the process, as was building trust in the process, in the people participating in the process, and in the information provided. The outcomes of such processes reinforce the importance of public input and research on public opinion, help to make an issue accessible to diverse audiences, support agency and industry program prioritization efforts, and encourage mutual education. The process provides an approach to enable translation of the concerns, benefits, and science surrounding an issue.

Two frameworks for communicating information to participants in biomonitoring studies were described. For a clinical ethics framework, health professionals decide whether results from a biomonitoring studies are clinically relevant. They establish clinically actionable levels prior to the start of study and if results are below these levels, they are not reported back to participants. However, it was noted that not providing all findings to study participants could be considered counter to current medical practice that encourages patients to be informed and to be proactive in directing their own health care. Participants may be able to process complex and uncertain findings and should have the option to decide whether or not to take action. The second framework, called community-based participatory research framework, is a collaborative effort among researchers, community members, and study participants in which decision-making is shared with both aggregate and individual report-back protocols. The researchers explain uncertainties associated with exposure methods and the results. In the NCS, NIH Study Centers are encouraged to work with Community Action Boards to identify issues of local interest that could be researched using NCS data. The Community Action Boards also provide input to the study design.



Masatoshi Kumamoto, JCI, Japan, and L.J. (Lynn) Frewer, University of Wageningen, The Netherlands

The speaker also described household exposure studies and the findings of interactions between cumulative impact from multiple exposures and vulnerabilities due to biological susceptibility and psycho-social stressors. A challenge is how to move away from chemical-specific assessments to cumulative risk approaches. Biomonitoring can help identify those who have high measurement values and where interventions are needed most, but for emerging

contaminants, the technology is outpacing the understanding of what impacts, if any, there are on human health. The message has to match the strength of evidence (Brody et al., 2007).

The NewGeneris (Newborns and Genotoxic Exposure Risks) project was described as a large-scale study of mother-child birth cohorts and biobanks that evaluates biomarkers of dietary exposure to genotoxic and immunotoxic chemicals and biomarkers of effects. The project goal is to evaluate the relationship between early-life exposures to chemicals and increased risks for childhood cancer and immune disorders. The program has a dedicated Dissemination and Communication office and its staff members identify potential messages resulting from a project, including ethics issues, identify target audiences and stakeholders, develop communication strategies, and conduct dissemination activities. For example, the study may have public health messages such as dietary components associated with disease risk, and messages regarding scientific advancements, such as improved methods for exposure assessment. NewGeneris has an External Advisory Board and its responsibilities include providing advice on information dissemination. The program uses a variety of communication venues including its Web site, newsletters, brochures, workshops, scientific symposia, and targeted, direct contact with stakeholders on a small scale. A group is also dedicated to ethics and is responsible for communicating to the families in compliance with the families' preferences identified during the consent process.

A presentation in this session described how the ICCA and the chemical industry are working to improve communications about its products. Efforts to enhance management of chemical products worldwide through a Global Product Strategy (GPS) include three aims related directly to communication: (1) improve flow of information; (2) share relevant information between industry and the public; and (3) communicate GPS internally and externally. ICCA's Chemical and Policy Health Issue Group set goals for 2020 to establish a base set of information to conduct safety assessments of chemicals in commerce, build capacity to implement best assessment practices and management methods, work across value chain to encourage suppliers and customers to accurately evaluate risk and enhance performance, and share publicly relevant product information with governments and the public. The benefits include harmonization to reduce trade barriers and improve competitive landscape across the globe, better access to relevant product safety information, and improvements in credibility and trust in the chemical industry.

The ICCA is currently developing an information portal for exchange of product-related and substance information, such as GPS safety summaries, for co-producers, governments and the public that is free of charge. In the Phase 1 portal of development, safety summaries will provide compilations of relevant risk characterization and risk management information; however, they are not intended to replace technical information, such as material safety data sheets. Phase 2 will include the exchange of study data, but will include a fee for this type of information. Because the group is sensitive to the challenges of Web access in developing countries, research for alternative information dissemination methods is underway.

## ***Risk Perception and Risk Communication***

A presentation described how risk perception is not based on quantitative measures. Rather, risk perception is based on qualitative characteristics, such as controllability and fear as well as the factors of dread and unknown. People can use simple decision rules to understand risk and often reduce it to a single characteristic. For example, the affect heuristic model, in which a human being's feelings influence their decision-making, suggests that people rely on mental images and whether they are positive or negative (Finucane et al., 2000); high risk is perceived with negative images.

The speaker explained that trust is another major determinant in risk perception because loss of trust can lead to an increased perception of risk (Earle et al., 2007). The speaker described two processes in risk perception that usually work together and that are situation-dependent: (1) spontaneous processes that involve trust, gut feelings, and are automatic and fundamental versus (2) elaborative processes that require cognitive effort, common sense, and decision rules. Social trust relies on a belief in shared values; social trust can increase if few differences exist. Prior experience can also affect confidence and trust levels for subsequent interactions and distrust can happen when uncertainty is not acknowledged. Transparency is critical; withholding information increases distrust and increases the perception of risk.

Risk communication was also discussed as an approach to bridge between the natural and social sciences. The speaker introduced the presentation by noting that impact assessment is increasingly focused on both risks and benefits and that consumer decision-making often involves a trade-off between perceived risk and benefit. The speaker described a perpetual divide between consumers and experts on their perceptions about a variety of areas, including risk management approaches and priorities, the media, and the concept of uncertainty. The question was raised whether communication could provide a bridge between this perpetual divide. An example of loss of public trust was described: the 1999 dioxin controversy in Belgium in which a food chain was contaminated with dioxin. The government acted to manage the risks and did not notify the public until the story was revealed in the news media. The outcomes were that environmental interest groups became the only source of information about dioxins and the perception emerged that the truth was hidden to promote the vested interests of the regulators and industry.

However, it has been found that people use benefit and risk information to reinforce what they already believe, but that exposure to risk or benefit information can also depolarize attitudes. That is, benefit and risk information tends to make negative attitudes less negative and positive attitudes less positive. Balanced risk-benefit information can increase risk perception and reduced attitude ambivalence. Regarding the new technologies, information needs to be communicated in a

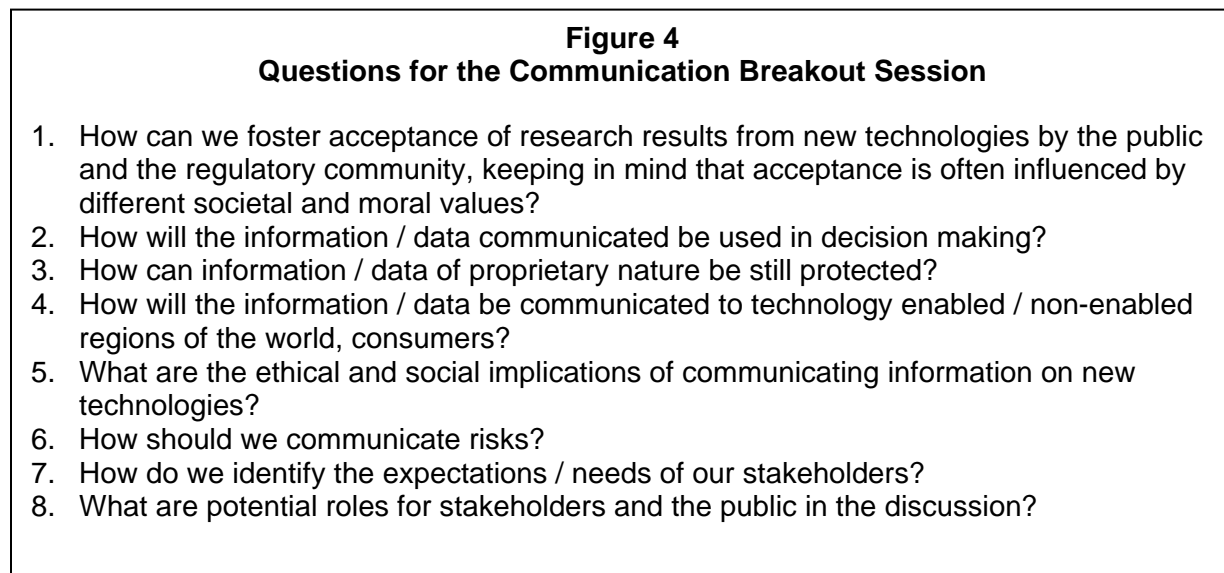


Maurice Whelan, Institute for Health and Consumer Protection, Joint Research Centre, European Commission, Italy

transparent way because limiting the discussion only to its benefits may be perceived by stakeholders as though the communicator is hiding the truth about risks. Information has little value if the communicator has lost the trust of the audience, and once lost, it is difficult to rebuild. Balanced risk-benefit communications are essential.

### *Panel Discussion*

To conclude this breakout session, participants were asked to consider the questions summarized in Figure 4.



The discussions emphasized that effective communication requires proactive audience analysis, planning, and message testing, all of which can demand significant effort. Risk communications should be designed for diverse audiences and targeted to different groups of individuals with similar values and characteristics. Good examples of this approach include health education campaigns to reduce obesity, smoking, and diabetes complications. Often with respect to chemical risk, the message is nuanced, neither safe nor unsafe, although the media and public tend to prefer the latter. Risk comparisons can also be helpful for stakeholders to understand implications. A suggested method to help the public to better understand risk would be use of a simple summary risk meter by researchers. Numeracy, meaning the quantitative literacy or skill with numbers, could also be included when developing communication materials. The lower the level of numeracy required to interpret the message, the more likely that the message would be understood.

The group discussed whether opportunities for best practices or standard operating procedures for risk communication could be established. It was agreed that some general recommendations for risk communications are available, but that the solutions are never one-size-fits-all. They acknowledged that it would be helpful to have general guidelines, but several people suggested that it would be more cost-effective to carefully analyze the audiences, craft messages that include both the good and the bad news, and then test the messages.

The group acknowledged in its discussions that the media are better at reporting bad news than good news. Benefits tend to be taken for granted, while preventative approaches are often difficult to promote and publicize. Another challenge and growing phenomenon for risk communication that must be addressed is the viral spread of misinformation through e-mail, blogs, and other sources.

Biomonitoring can be a useful approach for communities that want to track exposures, determine the extent of measured levels among the study population and potentially leverage governmental support and industry action regarding resolution of the concerns. But, as noted by the presenters of the Boston Consensus Conference summary, concerns exist that people could be stigmatized and experience discrimination. Concerns also discussed were that environmental disparities may become less compelling if drowned out by scientific analysis and that the potential exists for misuse of stored study samples in the future.

Risk-benefit communication is an emerging approach that holds promise, but it is still new. Consumer decision-making often involves a trade-off between perceived risk and benefit. Research has made progress in risk communication and perception, but there is a need to move from risk communication to risk-benefit communication. Although people consider risk information more important than benefit information, researchers are proposing new models to integrate risk and benefit metrics at the assessment phase as well as evaluating differences among cultures for considering trade-offs. A recommended follow up to this session would be to develop best practice points or what to do and what not to do, with the benefit of context through case study or scenario examples.

An overall conclusion of the group was that communication frameworks must integrate risk-benefit perspectives and incorporate cultural and value differences if they are to effectively deliver results from emerging research. Establishing trust among scientists, stakeholders, and decision-makers will be a fundamental priority for fostering acceptance of research results from the new technologies.

#### **4.0 Actualizing Innovations in Biological, Exposure, and Risk Sciences**

During the closing plenary session of the workshop, speakers addressed the challenges presented by actualizing the innovations in biological, exposure, and risk sciences discussed during the workshop. The speakers noted that the approaches selected should address the universe of chemicals that are relevant for evaluation, the exposure characterization issues, and how risk-based decision-making will be conducted by regulators, communities, and individuals. Efforts in each of these areas will be needed to move risk assessment forward to meet new demands for relevant risk information for



Thomas Hartung, Johns Hopkins Center for Alternatives to Animal Testing, USA

approaches to protect human health and the environment in the 21<sup>st</sup> century.

Chemical safety evaluations for human health and ecological risks are required under United States laws such as the Toxic Substances Control Act, the Federal Insecticide, Fungicide and Rodenticide Act, the Federal Food, Drug and Cosmetics Act, the Food Quality Protection Act, and the Endangered Species Act; tens of thousands of regulatory decisions in the United States and Europe are made annually based on these regulations. Under the REACH legislation, it is estimated that more than 144,000 substances will be registered and evaluated. At U.S. EPA, traditional approaches to health risk assessments, such as those using *in vivo* animal data, are transitioning towards new integrative and predictive 21<sup>st</sup> century techniques that will potentially increase the efficiency and effectiveness of toxicity testing and risk assessment. Computational tools, while not new, are now being used to evaluate and to prioritize follow-up actions, such as efficient and focused *in vivo* testing on identified priority substances. Important issues to be addressed include the continuing challenges of reconciling reductionist versus systems approaches; deterministic versus stochastic conceptualizations; validation at multiple levels; remaining open to future technologies; and ensuring methodologies are proven yet also widely accessible and deployable. Evidence-based approaches, such as Klimisch scores to assess the quality of toxicological data, will aid the progression of toxicology towards a more systems-based approach.

The challenge of assessing chemicals with limited data will be addressed through near-term and longer-term goals. In the near-term, integrated approaches to testing and assessment are needed to create efficient and credible means to predict toxic potency and exposure levels and to focus information needs on the areas of greatest concern. Over the longer term, goals must include addressing the challenge of reducing uncertainty, using tools such as ‘omics’ technologies, PBPK modeling, and improved exposure modeling and assessment, with a greater reliance on hypothesis and mechanism-based assessments. Regulatory agencies and international partnerships stand poised to play a large role in advancing collaborative research agendas and many other aspects of capacity building for this paradigm shift in chemical risk assessment. In addition, stakeholders will need to be engaged, communication will need to address questions of relevancy and impact, and processes will need to be transparent.

Consideration of the *exposome*—an individual’s total exposure from conception through life—as a new approach to exposure assessment will require prioritization tools that efficiently screen and capture environmental exposure scenarios. PBPK and human exposure modeling will increase the strength of risk assessments by extrapolating *in vitro* data to tissue doses that may occur in humans. Methods will include the continued development and use of biomarkers to enable tracking of chemical exposure and early effects and aid in identifying host susceptibility. Exposomics will be characterized by multiplexed, sensitive, quantitative, high-throughput technologies that will be minimally invasive, such as collection of human blood samples. A National Academies of Science public meeting scheduled for December 2009 will explore the concept of the exposome and its relevance to epidemiology of cancer and other diseases.



Vicki Dellarco, U.S. EPA,  
USA

## 5.0 Summary

A major objective for the 2009 ICCA-LRI Workshop was to provide a forum for discussions and interactions among diverse stakeholders on the three workshops themes of new technologies, exposure science, and communication and their relevance to current issues in chemical management and public health. Key findings and recommendations from the workshop are summarized below:



ICCA-LRI Planning Group Chair, Janet Mostowy, Bayer Corporation, USA

- Advanced technologies and the ‘omics’ offer great promise as alternatives to traditional toxicity testing strategies. Genomic tools are rapidly evolving and have the potential to dramatically change how chemical risk assessment is done; however, integration and interpretation of the new data using bioinformatic approaches remain as key challenges.
- Accurate assessment of real-world environmental exposures is an outstanding and largely unmet challenge that must be resolved to produce meaningful toxicological information that can appropriately inform risk assessments.
- Establishment of trust among scientists, stakeholders and decision-makers is a fundamental priority for fostering acceptance of research results from the new technologies.
- Communicating the relevant findings from the deluge of new scientific data to the public and involved stakeholders is a current challenge. Effective communication of the results from the complex data sets will be essential for building trust among stakeholders.
- Making sense of the emerging data requires integration of heterogeneous types of information and knowledge across many disciplines – building capacity for trans-disciplinary research will be essential.
- Data from exposures in the low-dose range are needed to improve our understanding of biological responses to everyday exposures to chemicals and activation of response pathways in cells and organisms across the dose-response continuum.
- Risk and health assessment systems must evaluate and account for genetic variability among populations and relate this variability to exposure. Variability between individuals and among populations, as well as differences in susceptibility due to age or health status, can also contribute significantly to variation in risks related to chemical exposures.
- Cumulative and integrated exposure assessments are emerging as a new norm; this thinking must be considered and incorporated into the exposure assessment component during design of risk assessment strategies.
- Statistical tools are available to optimize exposure data collection and analysis – all data points need not be collected from each individual to develop the exposure landscape. Application of appropriate statistical methods to the data generated by the exposure assessment and ‘omics’ studies is essential.
- ‘Omics’ can provide important new tools for exposure assessment to improve understanding of the global biological landscape.

Communication frameworks must integrate risk-benefit perspectives and incorporate cultural and value differences if they are to effectively deliver results from emerging research to stakeholders and decision-makers. ICCA-LRI workshops are designed to foster interactions among researchers and stakeholders that can improve the scientific basis for policymaking and to support consensus building that can advance the risk assessment process. As in previous years, the 2009 workshop provided a venue for highlighting ICCA-LRI as a leader and knowledge partner among scientific and regulatory experts and for directly addressing many of the complex scientific and regulatory challenges faced by the industry as it advocates for sound chemical management policies. Additional information about the ICCA-LRI, its research programs, publications and other activities can be found at our Web site ([www.icca-chem.org](http://www.icca-chem.org)).

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## Appendix A: Participant Affiliations

American Chemistry Council	ICF International
American Petroleum Institute	Imperial Oil Limited
Arch Chemicals, Inc.	International Isocyanate Institute
BASF SE	Israel Ministry of Health
Battelle	Japan Chemical Industry Association
BAYER AG	Johns Hopkins University
Bayer CropScience AG	Max Planck Institute for Molecular Genetics
Bayer MaterialScience AG	National Hellenic Research Foundation
Boston University, School of Public Health	National Institutes of Health, USA
Canadian Chemical Producers Association	National Institute for Health and Welfare, Finland
Carleton University	Oregon Health & Science University
Celanese Company	Pacific Northwest National Laboratory
Centers for Disease Control and Prevention	Procter and Gamble Company
Connecticut Department of Public Health	S.C. Johnson & Son, Inc.
CSIRO Mathematical & Information Sciences	Shell Health
Dana-Farber Cancer Institute, Harvard School of Public Health	Showa Pharmaceutical University
Dow Chemical Company	Silent Spring Institute
Dow Corning Corporation	Sumitomo Chemical Co., Ltd.
DuPont	Summit Toxicology, LLP
DuPont Engineering	The Hamner Institutes for Health Sciences
Eastman Chemical Company	The LifeLine Group, Inc.
ETH Zurich	United States Environmental Protection Agency
European Commission, Joint Research Centre	United States Food and Drug Administration
ExxonMobil Petroleum and Chemical Genedata	United States Government Accountability Office
George Washington University Law School	University of Aarhus
Helmholtz-Zentrum München	University of California, Berkeley
Human Health Sciences	University of Leicester
Humane Society of the United States of America	University of Medicine and Dentistry of New Jersey
	University of Michigan
	University of North Carolina – Chapel Hill
	University of Wageningen

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## Appendix B: Final Agenda

### Workshop Co-Chairs:

Elaine Cohen Hubal, Environmental Protection Agency, United States  
Richard Phillips, ExxonMobil Petroleum and Chemical, Belgium

### Tuesday, June 16, 2009

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7:00am – 8:00am Registration and Continental Breakfast

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8:00am – 8:20am Welcome, workshop objectives, and expectation of outcome

- **Elaine Cohen Hubal**, Environmental Protection Agency, USA
- **Richard Phillips**, ExxonMobil Petroleum & Chemical, Belgium

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### Plenary Session I: The Context

8:20am – 10:00am *Session Chair:* **Elaine Cohen Hubal**, Environmental Protection Agency, USA

*Speakers:* (25 minutes each, including Q&A)

Relating science and risk assessment

- **Elke Anklam**, Institute for Health and Consumer Protection, Joint Research Centre, European Commission, Italy

Non-animal methods of toxicity testing: From adjuncts to alternatives to the dominant paradigm?

- **Martin Stephens**, Humane Society of the United States, USA

Parking the Lexus under the olive tree

- **John Young**, Ministry of Health, Israel

Cultural cognition of the risks and benefits of nanotechnology: A case study

- **Donald Braman**, George Washington University Law School, USA
- 

10:00am – 10:30am Morning Break

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### Plenary Session II: Setting the Stage for the Parallel Breakout Sessions (*Willow Room*)

10:30am – 1:00pm *Session Chair:* **Tina Bahadori**, American Chemistry Council, USA

*Speakers:* (25 minutes each, including Q&A)

Does exposure imitate art?

- **Elaine Cohen Hubal**, Environmental Protection Agency, USA

Conceptualization, generation, and interpretation of high-throughput screening data in the Tox21 program

- **Christopher Austin**, National Institutes of Health (NIH) Chemical Genomics Center (NCGC), USA
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**Plenary Session II: Setting the Stage for the Parallel Breakout Sessions (continued)**

Genetic susceptibility: The link between environmental exposure and disease

- **John (Jef) French**, NIH, National Institute of Environmental Health Sciences (NIEHS), USA

Health risks in the headlines, the news cycle's love-hate relationship with risk communication

- **Kathryn O'Hara**, Carleton University, Canada

Outcomes of the ToxCast™ data analysis summit: Challenges in transforming toxicity testing from *in vivo* to *in vitro*

- **Richard Judson**, Environmental Protection Agency, USA

A geneticist's perspective on sensitive subpopulations, individual differences, polymorphisms, gene-environment interactions, and related issues

- **Thomas Meitinger**, Helmholtz Research Center, Germany

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1:00pm – 2:00pm

**Lunch**

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**Parallel Breakout Sessions**

2:00pm – 5:00pm

**Session 1: Advanced Technologies**

(including a 25 min  
**Afternoon Break**)

*Session Chair:* **Russell Thomas**, The Hamner Institutes for Health Sciences, USA  
*Rapporteur:* **David Rouquié**, Bayer Crop Science, France  
*Recorder:* **Ami Parekh**, ICF International, USA

Description of breakout session and charge to participants (5 minutes)

- **Russell Thomas**, The Hamner Institutes for Health Sciences, USA

*Speakers:* (30 minutes each, including Q&A)

Interpreting genomics data to understand the mechanism of toxicity

- **John Quackenbush**, Harvard School of Public Health, USA

An integrated *in vitro* and computational approach to define the exposure-dose-toxicity relationships in high-throughput screens

- **Russell Thomas**, The Hamner Institutes for Health Sciences, USA

Interpreting genomics data: Integrated databasing in the European framework toxicogenomics projects

- **Jochen Koenig**, Genedata, Switzerland

Connectivity mapping for early toxicity recognition using the FP6 InnoMed PredTox data

- **Timothy Gant**, University of Leicester, UK

Interpreting genomics data by identifying functional modules

- **Ralf Herwig**, Max Plank Institute for Molecular Genetics, Germany
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## Parallel Breakout Sessions (continued)

2:00pm – 5:00pm

### Session 2: Exposure Science

(including a 25 min  
Afternoon Break)

*Session Chair:* **Herman Autrup**, University of Aarhus, Denmark

*Rapporteur:* **Annette Guiseppi-Elie**, Dupont, USA

*Recorder:* **Alexis Castrovinci**, ICF International, USA

Description of breakout session and charge to participants (5 minutes)

- **Herman Autrup**, University of Aarhus, Denmark

*Speakers:* (25 minutes each, including Q&A)

Exposure modeling: Setting the stage:

- **Olivier Jolliet**, University of Michigan, USA

Linking advanced chemical toxicity testing and population exposures

- **Ruthann Rudel**, Silent Spring Institute, USA

Extrapolation modeling and computational tools

- **Louise Ryan**, CSIRO Mathematical & Information Sciences, Australia

Understanding the impact of prenatal arsenic exposure through transcriptomics

- **Rebecca Fry**, University of North Carolina – Chapel Hill, USA

Systems biology and the mechanistic indicators of childhood asthma

- **Stephen Edwards**, Environmental Protection Agency, USA

Predictive exposure science, environmental bioinformatics, and computational toxicology

- **William Welsh**, University of Medicine & Dentistry of New Jersey, USA

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2:00pm – 5:00pm

### Session 3: Communication

(including a 25 min  
Afternoon Break)

*Session Chair:* **Melanie Bausen**, BASF - The Chemical Company, Germany

*Rapporteur:* **Peggy Geimer**, Arch Chemicals, USA

*Recorder:* **Kimberly Osborn**, ICF International, USA

Description of breakout session and charge to participants (5 minutes)

- **Melanie Bausen**, BASF - The Chemical Company, Germany

*Speakers:* (30 minutes each, including Q&A)

Making National Health and Nutrition Examination Survey (NHANES) data available

- **Jennifer Madans**, National Center for Health Statistics, CDC, USA

Boston Consensus Conference on Biomonitoring: Video and Follow-up (40 minutes, including Q&A)

- **Madeleine Scammell and Jessica Nelson**, Boston University, USA
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**Parallel Breakout Sessions (continued)**

2:00pm – 5:00pm

**Session 3: Communication (continued)**

(including a 25 min  
**Afternoon Break**)

The underlying causes of susceptibility, environmental justice, and the importance of communicating environmental health information

- **Rachel Morello-Frosch**, University of California – Berkeley, USA

Making National Children’s Study (NCS) data available to the public and the associated issues

- **Jennifer Park**, NIH, National Institute of Child Health and Human Development (NICHD), USA

Discussion among session participants (20 minutes)

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5:00pm – 6:00pm

**Break**

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6:00pm – 7:00pm

**Reception and Poster Viewing**

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7:00pm – 9:00pm

**Group Dinner**

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**Wednesday, June 17, 2009**

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7:00am – 8:00am

**Continental Breakfast**

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**Parallel Breakout Sessions**

8:00am – 11:15am

**Session 1: Advanced Technologies**

(including a 25 min  
**Morning Break**)

*Session Chair:* **Timothy Gant**, University of Leicester, UK

*Rapporteur:* **David Rouquié**, Bayer Crop Science, France

*Recorder:* **Ami Parekh**, ICF International, USA

*Speakers:* (30 minutes each, including Q&A)

MicroRNAs as markers and modulators of toxicity

- **Timothy Gant**, University of Leicester, UK

Exploring inter-individual differences in toxicity responses using *in vitro* and *in vivo* approaches

- **Ivan Rusyn**, University of North Carolina – Chapel Hill, USA

Genetic polymorphisms and susceptible populations

- **Gary Ginsberg**, Connecticut Department of Health, USA

The promises, successes and setbacks in “-omic” approaches

- **Donna Mendrick**, Food and Drug Administration, USA
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**Parallel Breakout Sessions (continued)**

8:00am – 11:15am

**Session 1: Advanced Technologies (continued)**

(including a 25 min  
**Morning Break**)

Panel discussion (10 minute set-up by each of the discussion leaders listed below and 30 minute discussion by group)

*Discussion Leaders:*

- **James Bus**, The Dow Chemical Company, USA
- **Raymond Tice**, NIH, National Institute of Environmental Health Sciences (NIEHS), USA
- **Timothy Gant**, University of Leicester, UK

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8:00am – 11:15am

**Session 2: Exposure Science**

*Session Chair:* **Matti Jantunen**, National Institute for Health and Welfare, Department of Environmental Health, Finland

*Rapporteur:* **Annette Guiseppi-Elie**, Dupont, USA

*Recorder:* **Alexis Castrovinci**, ICF International, USA

*Speakers* (20 minutes each, including Q&A):

PBPK modeling and interpretation of biomonitoring data — Estimation of chemical concentrations in human bodies from their doses for animal studies

- **Hiroshi Yamazaki**, Showa Pharmaceutical University, Japan

Exposure and EPA's National Exposure Research Laboratory

- **Peter Egeghy**, Environmental Protection Agency, USA

*Speakers* (25 minutes each, including Q&A):

Predicting biologically relevant exposures (25 minutes, including Q&A)

- **Justin Teeguarden**, Pacific National Laboratories, USA

Dose reconstruction and extrapolation modeling (25 minutes, including Q&A)

- **Russell Thomas**, The Hamner Institutes for Health Sciences, USA

Consideration of “dose” in evaluation of ToxCast™ data: Use of biomonitoring and pharmacokinetic data (25 minutes, including Q&A)

- **Lesla Aylward**, Summit Toxicology, USA

Panel discussion

*Discussion Leaders:* (10 minute set-up by each of the discussion leaders listed below and 50 minute discussion by group)

- **Paul Price**, The Dow Chemical Company, USA
  - **Matti Jantunen**, National Institute for Health and Welfare, Department of Environmental Health, Finland
  - **Linda Sheldon**, Environmental Protection Agency, USA
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**Parallel Breakout Sessions (continued)**

8:00am – 11:15am

**Session 3: Communication**

(including a 25 min  
**Morning Break**)

*Session Chair:* **Corinna Weinz**, Bayer AG, Germany

*Rapporteur:* **Peggy Geimer**, Arch Chemicals, USA

*Recorder:* **Kimberly Osborn**, ICF International, USA

*Speakers:* (30 minutes each, including Q&A)

Dissemination of research outcomes to the scientific community and broader public for the EU NewGeneris project

- **Maria Botsivali**, National Hellenic Research Foundation, Greece

ICCA Global Product Strategy - Increased transparency for stakeholders and the public

- **Melanie Bausen**, BASF – The Chemical Company, Germany

Consumer behavior: Matching risk communication with risk perception

- **Vivianne Visschers**, Federal Institute for Technology Zurich, Switzerland

Risk communication: bridging between natural and social sciences

- **L. J. (Lynn) Frewer**, University of Wageningen, The Netherlands

Panel discussion (50 minutes)

*Discussion Leaders:* (5-10 minute set-up by each of the discussion leaders listed below)

- **Joy Hugick**, Centers for Disease Control & Prevention (CDC), USA
- **John Young**, Ministry of Health, Israel
- **Kathryn O'Hara**, Carleton University, Canada

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**Parallel Breakout Session Report Back**

11:15am – 12:30pm

*Session Chair:* **Bruno Hubesch**, CEFIC aisbl (European Chemical Industry Council), Belgium

*Speakers:* (15 minutes each, including Q&A)

- **David Rouquié**, Bayer Crop Science, France
- **Annette Guiseppi-Elie**, Dupont, USA
- **Peggy Geimer**, Arch Chemicals, USA

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12:30pm – 1:30pm

**Lunch**

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### Plenary Session III: Actualizing Innovations In Biological, Exposure and Risk Sciences

1:30pm – 3:30pm

*Session Chair:* **Richard Phillips**, ExxonMobil Petroleum & Chemical, Belgium

*Speakers:* (30 minutes each, including Q&A)

Implications of the exposome for exposure assessment

- **S.M. Rappaport**, University of California - Berkeley, USA

Toward an evidence-based toxicology

- **Thomas Hartung**, Johns Hopkins Center for Alternatives to Animal Testing, USA

Meeting the needs of a paradigm shift – a regulatory perspective

- **Vicki Dellarco**, Environmental Protection Agency, USA

Exploiting innovations in hazard assessment through integrated testing strategies

- **Maurice Whelan**, Institute for Health and Consumer Protection, Joint Research Centre, European Commission, Italy

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3:30pm – 3:45pm

Workshop Closing Comments

- **Janet Mostowy**, ICCA-LRI Planning Group Chair, Bayer Corporation, USA

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3:45pm – 4:00pm

**Afternoon Break / Adjourn**

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### Appendix C: List of Poster Presentations

	<b>First Author Affiliation</b>	<b>Presenter Affiliation</b>	<b>Abstract Title</b>
1	L. Aylward <i>Summit Toxicology, LLP, USA</i>	L. Aylward <i>Summit Toxicology, LLP, USA</i>	Consideration of “dose” in evaluation of ToxCast™ data: Use of biomonitoring and pharmacokinetic data
2	M. Breen <i>National Exposure Research Laboratory, U.S. EPA, USA</i>	M. Breen <i>National Exposure Research Laboratory, U.S. EPA, USA</i>	Exposure Model for Individuals (EMI) in air pollution health studies: Development of residential indoor air quality model for PM <sub>2.5</sub>
3	S. Edwards <i>National Health and Environmental Effects Laboratory, U.S. EPA, USA</i>	S. Edwards <i>National Health and Environmental Effects Laboratory, U.S. EPA, USA</i>	Toxicity pathway-based mode of action modeling for risk assessment
4	S. Flack <i>University of North Carolina at Chapel Hill, USA</i>	L. Nylander-French <i>University of North Carolina at Chapel Hill, USA</i>	Quantitative plasma biomarker analysis in 1,6-hexamethylene diisocyanate (HDI) exposure assessment
5	L. Trelles Gaines <i>University of North Carolina at Chapel Hill, USA</i>	L. Nylander-French <i>University of North Carolina at Chapel Hill, USA</i>	Urine 1,6-hexamethylene diamine (HAD) levels among workers exposed to 1,6-hexamethylene diisocyanate (HDI)
6	M. Morgan <i>National Exposure Research Laboratory, U.S. EPA, USA</i>	M. Morgan <i>National Exposure Research Laboratory, U.S. EPA, USA</i>	Biomonitoring: Current tools and approaches for assessing human exposures to non-persistent chemicals
7	K. Waters <i>Pacific Northwest National Laboratory, USA</i>	K. Waters <i>Pacific Northwest National Laboratory, USA</i>	Modular network modeling of cell stress response from integrated microarray and proteomic expression data
8	N. Wilson <i>Battelle Centers for Public Health Research and Evaluation, USA</i>	N. Wilson <i>Battelle Centers for Public Health Research and Evaluation, USA</i>	Children’s pesticide exposures: Aggregate potential doses and urinary biomarkers
9	B. Sonawane <i>National Center for Environmental Assessment, Office of Research and Development, U.S. EPA, USA</i>	B. Sonawane <i>National Center for Environmental Assessment, Office of Research and Development, U.S. EPA, USA</i>	Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches