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

Twenty-First Century Approaches to Toxicity Testing, Biomonitoring, and Risk Assessment Workshop Summary Report

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List of Acronyms

ACC	American Chemistry Council
BE	Biomonitoring Equivalent
CDC	Centers for Disease Control and Prevention
Cefic	European Chemical Industry Council
ETS	Environmental Tobacco Smoke
EU	European Union
GerES	German Environmental Survey on Children
HBM	Health Based Monitoring
HTS	High Throughput Screening
ICCA	International Council of Chemical Associations
JCIA	Japan Chemical Industry Association
KiGGS	German Health Interview and Examination Survey for Children and Adolescents
NGO	Non-governmental organization
NRHEEC	National Reports on Human Exposure to Environmental Chemicals
JCIA	Japan Chemical Industries Association
LRI	Long-Range Research Initiative
NRC	National Research Council
Q(SARs)	(Quantitative) structure-activity relationships
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
RKI	Robert Koch Institute
UBA	Umweltbundesamt (the German Federal Environment Agency)
U.S.	United States
U.S. EPA	U.S. Environmental Protection Agency
USA	United States of America

EXECUTIVE SUMMARY

The International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) sponsored a workshop, titled *Twenty-First Century Approaches to Toxicity Testing, Biomonitoring, and Risk Assessment*, on June 16 and 17, 2008 in Amsterdam, The Netherlands. The workshop focused on research, development, and application of the advances in new technologies for toxicity testing and for biomonitoring; approaches for effective communication of the data generated by these new technologies; and understanding the relevance of the new data to human health risks. In essence, this was a *Call to Action* to bring together the intellectual and financial resources necessary to harness the potential of these new technologies towards improved public health decision-making. A poster session complemented the program, summarizing research from 20 projects conducted in Europe and Asia that related to the key themes of the workshop.

The three topic areas for the workshop's plenary and breakout sessions were:

- Biomonitoring – Explored the links between biomarkers and environmental exposures and how new technological advancements, including biological or environmental monitoring and modeling, could facilitate interpretation of biomonitoring data.
- Advanced technologies – Reviewed new advances in toxicity testing/molecular screening and discussed how these approaches could produce information useful to risk assessment. Discussions included an emphasis on reference standards, dose-response issues and how the new technologies could foster a systems biology approach.
- Risk assessment – Discussed how applications of new technologies in biomonitoring and toxicity testing could facilitate public health decision making and communication of results to the medical community, the public and the media.

Workshop participants articulated their concerns that scientific approaches for interpreting and understanding the emerging data in a biologically relevant context clearly lag behind the rapid advancements in the new technologies. Research will be needed to mitigate these lags and to develop frameworks for communicating the information, even in a context of uncertainty. Key areas requiring research include improved understanding of response pathways, dose response, low dose effects, mode of action, susceptibility, and genetic polymorphisms; translation of data from biomonitoring and biomarker studies into health-relevant information; and better characterization of exposure information. The closing session of the workshop included presentations and recommendations that laid the groundwork for a path forward that modernizes risk assessment and for approaches to better inform decision-making related to public health and consumer issues.

The workshop successfully brought together a diversity of international expertise and perspectives to identify and help overcome the barriers to the success of these new technologies to enhance public-health decision making. The next workshop, currently planned for Spring 2009, will follow the same format with its overall theme to engage and build capacity for connecting the innovations in biological, exposure, and risk sciences.

1.0 INTRODUCTION

On June 16 and 17, 2008, the International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) sponsored a workshop entitled *Twenty-First Century Approaches to Toxicity Testing, Biomonitoring, and Risk Assessment* to stimulate discussions and interactions among participants regarding innovative approaches to the assessment of risk. The workshop focused on research, development, and application of recent advances in technologies for toxicity testing; communication of the data generated by these new technologies; and understanding the relevance of the new data to human health risks. This workshop was designed to bring together the intellectual and governmental resources that can foster the use of these new technologies to improve public health decision-making. The workshop was held in Amsterdam, The Netherlands and the attendees included 156 international scientists, public health and public policy professionals, and communicators from academia, governmental and non-governmental organizations (NGOs), and industry (see Appendix A for a list of participant affiliations).

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), respectively. In 2005, the ICCA-LRI identified interpretation of biomonitoring data as its highest priority research area. Since that time, the ICCA-LRI has taken a global leadership role in the interpretation of human biomonitoring data, particularly regarding its relevance to real world exposures. The core of its approach has focused on research and communication strategies that link with outreach activities to governments, NGOs, and the public. A key component of the communication and outreach strategies has been a series of public workshops (see Exhibit 1). These workshops were designed to complement ongoing research, ensure coordination in the implementation of the regional biomonitoring research programs, maintain engagement with public authorities, keep the industry's commitment in the public eye, and provide leadership to others working in this field.

Exhibit 1
Previous ICCA-LRI Biomonitoring Workshops and Goals

- *June 2005 in Paris, France* – to review the biomonitoring "issue" from the perspectives of product stewardship, policy/advocacy, communications, and science gaps
- *July 2006 in Minneapolis, USA* – to build consensus on research priorities that would guide both future LRI programs and those of other research organizations
- *September 2007 in Research Triangle Park, USA (in conjunction with the US EPA)* – to provide a context for discussion and exchange on the strengths and weaknesses of biomonitoring for the purpose of public health tracking, intervention, and protection

Based on the strong commitment by each of the regional programs to the LRI vision, the LRI has become recognized as an industry trademark in the public's eyes. Successful implementation of the ICCA global research strategy, thus far, can be attributed to the development of processes that increased the transparency and cohesiveness of the regional programs and created venues through which a 'one industry' approach could be developed. Another factor contributing to LRI's success was the cogency and timeliness of the research

directions that were selected and their relevance to the issues faced by the chemical industry and other international stakeholders.

Through its biomonitoring research program, the ICCA-LRI became increasingly aware of the critical importance that exposure information, and in particular information about environmentally relevant exposures, plays in meaningful interpretation of biomonitoring data. The ICCA-LRI recognized that relationships among biomonitoring, real-world exposures, and recent innovations in technology for toxicity testing could be synergized through a global coordination effort by LRI. Such a coordinated effort could provide great value to the chemical industry by improving the 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 would take a lead in fostering innovative approaches for the assessment of risk. Similar to the overall aim of the biomonitoring program, ICCA-LRI would focus on improving the understanding of dose, exposure, and ultimately the risks associated with environmental stressors. At present, human health risk assessments are generally based on results from toxicity studies using exposure concentrations that exceed real-world levels by orders of magnitude. The majority of health scientists agree that these high doses are not scientifically relevant for interpreting possible risks from the low-level exposures to chemicals that can occur in everyday life.

The focus of the new research program is advancement of the current risk assessment framework towards approaches that can improve the understanding of environmentally-relevant doses. The advent of new technologies, including toxicogenomics, proteomics, metabonomics, transcriptomics, and associated bioinformatics technologies, is primed to enable a new paradigm in toxicity testing that can facilitate understanding of the potential health implications from exposures to chemicals for the general public and the chemical industry.

The agenda for the two-day workshop is provided in Appendix B. The first day of the workshop featured plenary session presentations by invited speakers that set the stage for the additional presentations and discussions later in the day during the parallel symposia. These symposia included speakers on selected topics and panel discussions. The three parallel symposia focused on the following topics: human biomonitoring, advanced technologies, and risk assessment. A poster session also held in the evening of the first day that showcased biomonitoring research from 20 projects conducted in Europe and Asia related to genomics, toxicity testing, exposure science, and the interpretation of biomonitoring data. A list of the posters presented is included in Appendix C. The parallel symposia concluded on the second day with rapporteurs from each session presenting summaries of their respective deliberations and conclusions at a general session of the workshop. The workshop concluded with presentations that focused on future directions for the field of risk assessment.

These proceedings are a summary of the presentations, discussions, and overarching themes from both the plenary and parallel symposia sessions at this workshop. They are intended to summarize the main themes of the discussions and provide a starting point for further communications among all parties regarding twenty-first century approaches to toxicity testing, biomonitoring, and risk assessment.

2.0 SESSION HIGHLIGHTS

The need for innovative approaches to improve the quality of human life and protect the environment has never been more critical and advances in science and technology are essential for achieving this objective. Today, the general public has concerns about possible adverse health effects from chemicals present in the products they use every day. The chemical industry recognizes the importance of promoting consumer confidence in its products through implementation of high standards for its corporate activities as well as though accurate and responsible communication to the general public (see Exhibit 2).

Exhibit 2
Promoting Consumer Confidence
(Adapted from Duncan, 2008)

Science and technology creates solutions; however, they also produce risks to be managed. In general, people do not have the time and knowledge to evaluate the balance of these solutions and risks. As a result, information overload may result in anxiety, fear, and mistrust.

It is important to recognize that reactions and motivations differ depending on a person's view of the world; therefore, industry must work to understand and address these various motivations in order to command continued trust in their products. Ways in which industry can build consumer confidence include:

- Visibly placing the highest priority on safety and environmental protection
- Making safety decisions independent of commercial considerations
- Conducting clear and transparent risk assessments
- Responsibly communicating to the general public
- Measuring and mitigating impacts

Industry, regulators, academics, and NGOs, both nationally and internationally, can all benefit from collaborative efforts to support innovations aimed at improving the quality of human life and protecting the environment. Such collaborations can foster the use of new approaches for toxicity testing, biomonitoring, and risk assessment. These collaborations can also be a source of recommendations for new research priorities, improvements in criteria for data interpretation, and updated methods for responsible communication of potential risks to the general public.

A summary of the plenary sessions and highlights of the presentations are presented in the sections that follow. A list of the speakers and their talks is included in the workshop agenda, which is provided in Appendix B.

2.1 Providing the Context of the Meeting

The overall theme of the speaker presentations in this opening session was the importance of dealing sensibly with both present and future environmental health risks. Presentations focused on the need for a paradigm shift away from current risk assessment and decision-making approaches towards ones that are more time and cost effective. Describing complex and controversial risk problems in a coherent and meaningful way is always challenging. For this reason, it is important to develop an overarching strategy for addressing environmental health concerns that incorporates relevant scientific and decision-making expertise, as well as meaningful guidance in dealing with complex scientific information and communication. Without a clear political framework for decisions related to risk, the potential

for decision-making to weaken in the face of complex issues can exist. Presentations in this opening session described frameworks that are being developed in several countries to specifically address this issue.

In the Netherlands, Dutch policy has motivated the formulation of a new risk-based decision-making framework to deal with real world risks, perceptions, and irrationalities based on a practical approach. An analysis of trends through past years indicates that complex and persistent problems are broadening the scope of issues to be assessed, information technology is evolving (i.e., providing better access to information and misinformation), scientific methods are advancing, and new issues are emerging. Presently, a number of different ideas, views, and indicators are used by various stakeholders to evaluate risks. As environmental health problems become more complex and societal costs and benefits become increasingly important, the development of common indicators to describe the depth and breadth of these complex environmental health problems and situations is needed. Key elements of this framework include:

- Ensuring transparency for political decisions;
- Explicitly defining the responsibilities for governments, industry, and the public;
- Weighing societal costs and benefits against hazard/risk;
- Strengthening the role of the public in the decision-making process; and
- Accounting for possible accumulation of risks.

For complex environmental health problems with large societal costs, as well as controversy, and uncertainty, risk governance more than traditional risk assessment and management is needed.

In the United States (U.S.), the traditional exposure-response approach for risk assessment is also evolving. Two recent National Research Council (NRC) reports call for a paradigm shift away from the traditional morbidity and mortality endpoints used in toxicity testing towards the concept of perturbation of response pathways (NRC 2007a, NRC 2007b). This paradigm shift will involve the use of computational toxicology and high throughput screening (HTS) assays that use *in vitro* cell systems; it will potentially allow a much broader evaluation of the universe of environmental agents. This vision outlined in these reports will, however, require a substantial commitment of resources as well as and support from the scientific community, regulators, law-makers, industry, NGOs, and the general public. A research strategy will need to be developed collaboratively among the stakeholders. A successful strategy will incorporate coordination and sharing of databases and analytical tools, cataloging of critical response pathways for target organs, sponsorship of workshops to broaden scientific discussion and input into the research strategy directions. It should also include outreach to the international community, scientific training of end users of the new technologies, and support for activities related to the requirements for national and international regulatory acceptance of the new approaches. A key for implementing this vision will be effective communication, particularly for risk assessors, policy makers, and ultimately the general public.

2.2 Setting the Stage for the Parallel Symposia

The presentations in this session provided an overview of the three parallel symposia sessions that would follow on human biomonitoring, advanced technologies, and risk assessment; highlights from these presentations follow.

In Europe and the U.S., human biomonitoring is being employed by public health groups and physicians to identify emerging issues; determine sources of exposures, reference ranges, and societal use patterns; classify risk factors; and determine what actions should be taken at a policy and at an individual level. Because of these uses, emphasis has been placed on the inclusion of advanced technologies in biomonitoring programs to help with decision making and risk assessment.

The advanced technologies are becoming increasingly important as tools for evaluating chemical toxicities. Industry, member states, and the European Commission are now responding to the requirements of the recent Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation and the European Environment and Health Action Plan; both have placed large demands on *in vitro* and *in vivo* testing capacities. The newest amendment to REACH involves the promotion of alternative methods for toxicity testing. In response, several testing regimes are in development, including research projects Predictomics (2008), ReProTect (2006), and TOXDrop (2008). These methods employ novel *in vitro* techniques for determining chemical toxicity. One of the more interesting methods is the carcinoGENOMICS (2007) project, a high throughput genomics-based system for assessing genotoxic and carcinogenic properties of chemical compounds *in vitro*. This alternative to rodent bioassays can be employed to test genotoxic and non-genotoxic carcinogens and ultimately would be used to develop a battery of organ-specific genomics-based *in vitro* assays to be submitted to the European Centre for the Validation of Alternative Methods. Similarly, NewGeneris (2008) is a novel *in vivo* regime that will employ biomarkers of dietary exposure to genotoxic and immunotoxic chemicals, as well as biomarkers of early effects using mother-child birth cohorts and biobanks. All combined, these technologies are aiding in the EU's progression towards the use and application of human biomonitoring that integrates transcriptomics, proteomics, metabonomics, and bioinformatics.

Much like their EU counterparts, the U.S. Environmental Protection Agency (U.S. EPA) has turned to advanced technologies to address the increasing demands for toxicity testing by developing the ToxCast™ Research Program (U.S. EPA 2008a). This program was designed as a fully transparent and affordable science-based system for categorizing chemicals and decreasing reliance on high-cost *in vivo* testing. The ToxCast™ goal is to identify potential modes of action for each chemical, obtain the associated HTS assays, screen chemical libraries, and link results to *in vivo* effects, with an objective of refining the number of animal hazard identification and risk assessment tests necessary. Built-in duplicates and triplicates increase confidence and allow for quality assurance. During the first phase of program, U.S. EPA is analyzing 320 chemicals, primarily pesticides, through efforts that include data acquisition and mining, a data summit, and partnerships with other agencies.

3.0 SYMPOSIA REPORTS

The goal of the parallel symposia sessions on human biomonitoring, advanced technologies, and risk assessment was to initiate discussions among the participants from their various perspectives regarding the science basis for policies, how these new techniques play a role in risk assessment, and how to build consensus and move the risk assessment process forward. The role of new molecular biology techniques and their potential to improve our understanding of health impacts of various environmental stressors is continuing to develop and is increasingly prevalent in the media. Advancing the science and communicating both the new knowledge and knowledge gaps to the public requires a significant investment and deliberate attention. Developing policies that protect public health as this science evolves and is translated presents an important challenge.

The objectives and results of the group discussions are summarized in the three sections that follow.

3.1 Session 1: Human Biomonitoring

Biomonitoring data can improve our understanding of human exposures to a wide range of substances. It can provide evidence of human exposures to chemicals, establish a baseline of human exposures to environmental chemicals, identify subgroup populations that have higher levels of exposure and allow for tracking of exposure trends. As biomonitoring technology advances, more information is available to help public and private sector scientists, medical professionals and policy makers advance developments in public health and worker health and safety. An increased focus on early life testing and human variability and the shift from risk assessment to risk management are key components of the continuing biomonitoring research initiatives. The need for international information sharing has increased dialogue between national and local representatives and can provide locality cross-checks, individual subpopulation data, intervention research, and regional coordination.

The full potential of biomonitoring data cannot be realized without establishing links between biomarkers of exposure and actual environmental exposures. This parallel session explored the current progress regarding these links, as well as how advancement in technologies, such as biological and environmental monitoring and modeling, can further elucidate this connection and improve interpretation of human biomonitoring data. Potential applications for biomonitoring are summarized in Exhibit 3.

To showcase new developments and advancements in quantitative and qualitative interpretation as well as in applications for biomonitoring data, this session addressed three main themes: current use of biomonitoring in large population studies; reports on new biomonitoring data, new information on trends, and planning efforts; and updates on modeling and statistical approaches. These themes are further discussed in the following sections.

Exhibit 3
The Potential Use of Biomonitoring Data
(Adapted from Barr, 2008)

Biomonitoring data can potentially be used for the following purposes:

- Establishing reference values
- Determining which chemicals get into members of the general population and at what concentrations
- Identifying highly exposed populations
- Identifying susceptible populations
- Conducting trend analyses in levels of exposure
- Assessing the effectiveness of public health efforts to reduce exposure
- Setting priorities for chemical evaluation
- Setting priorities for research on human health effects
- Reducing the uncertainty in exposure assessment
- Determining if product stewardship and risk management efforts are warranted

Current Use of Biomonitoring Data in Large Population Studies

The first presentation of the session described two parallel large German population studies designed to obtain representative data on the health and development of children and adolescents: the German Health Interview and Examination Survey for Children and Adolescents (KiGGS; Robert Koch Institute [RKI] 2005) and the German Environmental Survey on Children (GerES; Umweltbundesamt [UBA] 2008). These studies were initiated in response to a lack of available children's health data. For example, little information existed regarding quality of life or life style, personal and social resources for health, subjective assessment of health, use of medical services and prevention programs, or risk behavior and knowledge. Data from both of these surveys now allow evaluation of relationships between environmental conditions and health of the children.

The KiGGS study (RKI 2005) was designed as a comprehensive, nation-wide, representative interview and examination survey for the age group 0 to 17 years. It was conducted from 2003 through 2006, and involved a total of 17,641 participants from 167 communities. The aim of this study was to collect data from each study subject including objective measures of physical and mental health as well as parent- or self-reported information regarding the subjective health status, health behavior, health care utilization, social and migrant status, living conditions, and environmental determinants of health (RKI 2005). Initial results indicated that respiratory allergic diseases were the predominant among the chronic somatic diseases afflicting German children and that with increasing age, the incidence of allergic diseases increased. Furthermore, when the percentage of sensitized children ages 14 to 17 years was evaluated, nearly 50 percent of the children were sensitized; sensitization increased with age and was influenced by gender with boys more often sensitized than girls. In terms of obesity, the results suggested that it is more prevalent in children from families with lower socioeconomic

status, while children with immigration background also demonstrated an increase in prevalence of obesity with increasing age. Additional results are forthcoming with two more phases of the KiGGS being conducted from 2008 through 2015.

The fourth survey of the GerES, GerES IV (UBA 2008) used a sub-sample of the KiGGS study population and included 1,790 children, 3 to 14 years of age, from 150 sampling locations (subjects were representative with regard to age, gender, community size and region). The objective of the GerES IV was to generate representative data on exposure to environmental pollutants, identify relevant exposure pathways, propose strategies on prevention and reduction of exposure, and evaluate environmental policy measures. The results from the GerES IV indicated the following:

- Children are exposed to various chemicals affecting reproduction and development;
- Persistent chemicals with chronic toxicity can be detected in every child living in Germany;
- Exposure levels are related to socioeconomic status;
- Health impact assessment should be supported by data from cohorts;
- Information and education can raise public awareness; and
- Exposure can be reduced by changes in behavior and political regulation.

Furthermore, concerning time trends between samples taken 1990/1992 and 2003/2006 it can be generalized from the results that mean concentrations of arsenic, cadmium, lead, mercury, metabolites of polycyclic aromatic hydrocarbons (1-hydroxypyrene), and pentachlorophenol in blood and/or urine of children aged 6-14 years decreased significantly (Schulz et al. 2007).

Reporting New Biomonitoring Data, New Information on Trends, and Planning Efforts

Ongoing biomonitoring studies in the U.S by the Centers for Disease Control and Prevention (CDC) was the next presentation topic. These large-scale population cohort studies have been valuable for elucidating links between health effects and environmental exposures as well as for detecting exposure trends in the U.S. An essential component for studies such as these is an established methodology for the collection and analysis of the samples so that data quality is consistent across the study. Important criteria for interpreting the biomonitoring data include, the specificity of the biomarker (chemical or route); biological persistence of the biomarker; analytical ability to accurately measure the biomarker; interpretability of the biomarker data (biomarker should be linked to exposure); and inter-and intra-person variability.

Currently, the CDC has several initiatives underway to assess trends in exposure, including the CDC's National Reports on Human Exposure to Environmental Chemicals (NRHEEC) and the National Health and Nutrition Examination Survey (NHANES) (CDC 2007).

The NRHEEC is an ongoing biennial biomonitoring study of exposures of the U.S. population to selected environmental chemicals that is based on results from urine and blood samples. The third report, released in 2005 (CDC 2005), provided data on exposures to approximately 265 chemicals; the next report is due to be released in the fall of 2008. This study accomplishes the following:

- Identifies the presence of environmental chemicals in the U.S. population
- Provides reference ranges for selected chemicals
- Identifies the prevalence of elevated levels of chemicals
- Identifies population groups with elevated levels
- Monitors changes in exposure over time for the U.S. population
- Assesses effectiveness of public health efforts to reduce exposures
- Provides exposure data for risk assessment
- Helps set priorities for human health effects research

The NHANES, which is the basis for NRHEEC, is managed by the CDC's National Center for Health Statistics. This survey is an ongoing annual survey that includes a home interview. For NHANES, the study population is a stratified, complex, multistage probability sample drawn from the civilian, non-institutionalized U.S. population; estimates are probability-based for the U.S. population. For example, from 1999 to 2004, NHANES collected results annually from approximately 5,000 participants in15 locations. The survey includes a detailed personal history, physical, and laboratory examinations. The two primary matrices used for NHANES biomonitoring are blood and its components and urine. Together, these two national studies provide public health experts with data to analyze temporal trends in exposure for several environmental contaminants, including lead, environmental tobacco smoke (ETS), persistent organic pollutants, brominated flame retardants, organophosphate insecticides, and other compounds. Trend analyses of the data can identify the effectiveness of exposure reduction efforts; removal of lead from gasoline and the corresponding decrease in blood lead levels is an excellent example. A clear benefit of the human data provided by these studies is that they can markedly decrease uncertainties associated with exposure assessments.

Another presentation focused on the use human biomonitoring data in the risk assessment process whenever possible. To accomplish this, sensitive, specific measurement parameters and reliable analytical methods for the collection and quality assurance of biomonitoring data are needed. In Germany, the human biomonitoring commission has developed a method for interpreting results from human biomonitoring studies that incorporates measurements of internal exposure as well as biochemical and biological effects using both reference values[1] and health based monitoring (HBM) values[2]. This method uses biomonitoring data to detect trends in exposure and to determine internal exposure. This approach can provide support for risk assessment and risk management decisions regarding chemicals.

[1] A reference value is a concentration of a substance in human biological material which is statistically derived from a defined group (representative) of the general population (e.g. 95thpercentile). While this value is not health based, it is highly accepted.
[2] HBM values are health based and include HBM I and HBM II values. A HBM I value is a concentration below which there is no risk for adverse health effects, but above which adverse health effects cannot completely be ruled out (it is an alert value), and an HBM II is an action value above which there is an increased risk for adverse health effects.

Modeling and/or Statistical Approaches for the Effective Use of Biomonitoring Data

Probabilistic reverse dosimetry was presented as a modeling approach for linking biomonitoring data to exposure. This approach involves probabilistic dose reconstruction at the population level and links biomarkers of internal dose to likely external exposures using human pharmacokinetic models. Probabilistic reverse dosimetry can be a useful approach in the absence of direct link between biomarker and health outcomes. This approach estimates the distribution of exposure levels in the environment that could account for measured biomarker concentrations in a population. These distributions can then be compared to regulatory exposure guidance values or no-effect levels in toxicity studies to put potential risks in context. While probabilistic reverse dosimetry shows great promise, there is still a need for additional population exposure characterization in terms of timing of collection of samples. The approach may also require information on the nature (sources, frequency, duration, etc.) of potential exposures – Surveys and questionnaires, like the ones described earlier (e.g., KiGGS and GerES), are helpful for gathering relevant information that might affect the study outcome (e.g., what people ate before sample collected).

Biomonitoring equivalents (BEs) were also discussed as modeling approach for linking biomonitoring data to exposure. BEs have been developed to leverage existing chemical risk assessment paradigm and chemical-specific pharmacokinetic information to answer the question of what biomonitoring level in blood, urine or other human biological media or tissues would be consistent with existing exposure guidance values. BEs provide a potentially valuable tool to help with risk prioritization and risk management decisions; prioritization of chemicals for risk assessment follow-up is the major application of BE values. The utility of BEs will improve as evaluations are conducted for additional chemicals. It is important to remember that BE values are screening guidelines for use by environmental health professionals and are intended for use only as tools to assist in the evaluation of general population or special population biomonitoring data. BEs are not intended for use in assessing biomonitoring data from individuals or for diagnostic purposes. BEs provide a tool for placing population-based biomonitoring results in a public health risk context. Ultimately, it is important to recognize, and to communicate to the public, that when biomonitoring levels exceed the BE, it carries the same functional definition as the underlying exposure guidance value; BEs are not bright lines between safe and unsafe exposures.

Conclusions and Responses to Breakout Questions

A group discussion on the questions presented in Exhibit 4 concluded this parallel session. Questions focused on improving the collection, interpretation, and application of biomonitoring data for the risk assessment and decision-making processes. The purpose of these questions was to stimulate discussions among session participants regarding the use of biomonitoring data to improve human health. The discussions focused on understanding the commonality and differences among the various programs, identifying areas for cooperation, maximizing value from the programs, and identifying a role for ICCA-LRI to address underemphasized areas.

Exhibit 4
Parallel Symposium 1 Questions: Human Biomonitoring

1. How do different organizations or groups that are responsible for public health decisions use biomonitoring data? How is information about the data being communicated?
2. How can the use of biomonitoring data in risk assessments be enhanced? (Discussion to include reverse dosimetry / reconstruction of exposure and forward dosimetry based on established exposure criteria)?
3. How can biomonitoring data be made more useful for risk management?

How do different organizations or groups that are responsible for public health decisions use biomonitoring data? How is information about the data being communicated?

Participants commented that biomonitoring data should not be used as a hazard identification tool because presence alone does not speak to the actual risk. Biomonitoring data should also not be used as evidence to deregulate or to ban chemicals based on hazard alone. In the U.S., a shift away from conducting risk assessments based on external dose is beginning to occur. The use of biomonitoring data can enable transitions towards risk assessments based on internal dose and from a hazard-based approach towards a risk-based approach.

One point of discussion was that government/regulators may be very risk averse and is hesitant to use biomonitoring data at all. However, efforts are underway to encourage the government to use biomonitoring data in a more effective manner and to interpret it within a health context. The successful use of biomonitoring data will involve effective communication. It is important to note that communication is very difficult when relating an individual's data to the population data. It is, therefore, necessary to communicate the acceptance of exposure, hazard, and risk and then have data that underpins this communication. The main goal should be to get ahead of the curve and biomonitoring research will help prioritize issues regarding chemicals so that it is possible to get and stay ahead of the curve.

Representatives from Germany shared that they are planning to use biomonitoring data in REACH. Human biomonitoring data will also be used in information campaigns and for raising consciousness in the general population (e.g., ETS) in order to demonstrate to people that they are putting themselves at risk by making certain choices. This will help people make an informed decision on what exposures they choose to undertake.

How can the use of biomonitoring data in risk assessments be enhanced?

When there is biological plausibility and an existing database of measured parameters, participants thought that the data should be mined to see if any associations exist to link biomonitoring data to outcomes. This type of effort will allow for establishment of effective methods of mining data and purposefully collecting logical, mechanistically relevant data. However, for this approach to work, more measurement/pathway analysis is needed. Using

exposure as an example, studies that have tried to cross-reference and find associations between what is found in body burden studies and what is present in home, dust, and other matrices sampled. Workshop participants believed that at the present time, this cannot be adequately accomplished without further measurement/pathway analysis versus what people have in their bodies and development of the necessary tools. In general, more and better biomarkers are necessary because there may not be one biomarker or approach that will be sufficient for all risk assessments, e.g. single chemical versus cumulative risk assessments.

How can biomonitoring data be made more useful for risk management?

The group discussed the importance of linking biomonitoring results back to exposure. Although this task will be a difficult, it should not stop the scientific and regulatory communities from moving forward. For example, if an integrated biomarker or a matrix of biomarkers for exposure to a class of compounds can be developed, this would allow for better risk assessment and, therefore, more effective risk management decisions for the general public. Regarding exposures to multiple chemicals, the participants believed that high throughput assays could be used for evaluating chemical interactions.

3.2 Session 2: Advanced Technologies

This session focused on the use of the new technologies to address health concerns about potential chemical exposures. Drivers in regulatory toxicology are currently focused on either priority setting for further testing, such as the U.S. EPA's ToxCast program, or new testing approaches that avoid the use of animals, such as the intelligent testing strategies in Europe. Participants acknowledged that current *in vivo* approaches for toxicity testing place a significant strain on government, industry, and other stakeholders. The international goal is to develop techniques that make testing more efficient, faster, and less expensive while taking into account individual susceptibility, multiple agents of exposure, and genetic variability. Other goals included improving information sharing and communication among all stakeholders, filling existing knowledge gaps and reviewing environmental risk assessment policies.

The objective for this session was to build on the plenary session presentations and to identify ways to use the new advances in toxicity testing/molecular screening (e.g., genomics, high throughput screening) and to discuss how these new approaches will produce information that can be used effectively in a risk-based context. Particular emphasis was placed on reference standards, dose-response issues, and how these technologies foster a systems biology approach.

Using new technologies for screening and prediction to improve risk assessment

Presentations on the first day of the advanced technologies session focused on new toxicity testing and molecular screening methods and how the new technologies are being used to improve prediction and risk assessment.

The first presentation outlined how the U.S., EPA's National Center for Computational Toxicology has joined with other government agencies, including the National Institutes of Health (NIH) Chemical Genomics Center and the Department of Health and Human Services'

National Toxicology Program, to form the ToxCast™ Program (U.S. EPA 2008a). This program is about three years old and is intended to help prioritize the toxicity testing of environmental chemicals. Under the program, high-throughput screening (HTS) is being conducted *in vitro* to test thousands of chemicals for biological activity. Researchers select chemicals with known or suspected toxicity in humans, identify response pathways, create testing systems (assays), and then conduct HTS on the chemicals to test for effects with the assays. The assay results will be published in NIH's chemical database called PubChem. An important current aim for this effort is to coordinate with other agencies and countries' efforts to achieve common goals more quickly. Some of the issues involve deciding on the universe of compounds and assays/pathways/targets/cellular phenotypes to test, figuring out the best way to conduct informatic analyses (e.g., culling of quantitative HTS data positives, comparison to animal toxicity data), and determining the appropriate use of quantitative HTS data in the prioritization process.

A second presentation described the EU Framework Programme 6 that has funded an integrated project on predictive toxicology called PredTox, a method that goes beyond simply testing (Genedata 2008). The project 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 the closer co-operation between industry and academia. Some of the challenges, however, include intellectual property issues and potential hidden competition, both of which complicate open data sharing.

Another presentation reviewed the expectations of scientists that genomic technologies have the ability to not just predict but can help with other aspects of risk assessment. The goal is to use mechanistic information and take advantage of *in vitro* models to get more and better information to be used to make decisions and reduce uncertainty in risk assessment. Genomics can have a significant impact on applied toxicology and risk assessment by enabling chemical screening based on biological activity, tailored testing based on mode of action, accelerated *in vitro* model development, and better dose-response assessment.

An important question raised during the session was whether genomic technologies can be used to identify and characterize the response of key events in the low dose region. Because the biological mechanisms that operate at high doses may not operate at low, environmentally-relevant doses, it is important to determine effects at low doses in order to make public health and policy decisions in the context of risk assessment. Researchers are hopeful that genomic data can help to address this question. Applying genomic tools to dose-response studies allows a broad survey of the transcriptional responses in various genes and the changes with dose. Integrating benchmark dose analysis also allows reference doses to be estimated for individual genes and functional categories. The first steps have now been taken to use the information in a genomics-based risk assessment, but there will be challenges to overcome along the way , e.g., determining which functional categories represent adverse versus adaptive effects, establishing what summary values to use for each category.

Conclusions and Responses to Breakout Questions

On the second day, the participants explored the topic of advanced technologies by addressing the discussion questions presented in Exhibit 5. The discussions were aimed at trying to understand the commonality and differences in the various programs discussed on the first day, to identify areas for cooperation across organizations and countries, to maximize value from the programs, and to identify a role for ICCA-LRI in addressing potential underemphasized areas.

Exhibit 5
Symposia Session 2 Questions: Advanced Technologies

1. What are the areas of opportunity or concern regarding how the new technologies will facilitate either objective (i.e., prioritizing or replacement)? What is the role of reference standards and validation for these two approaches? What is value of dose/exposure information as foundational reference standards for application of technologies to hazard and risk characterization? What differences might be expected in the use of new technologies for informing the strategies of the two approaches?

2. When is more data too much data? What are our current limitations on data understanding and how does this impact on the application of new technologies within chemicals testing programs?

Where will the new technologies fit within the testing process in the future? Will there be applicability at several levels, e.g., stratification, genetic, mechanistic, target-organ identification, dose-response assessment, estimation of long-term adverse outcomes?

3. Can new technologies inform existing operation assumptions of toxicity testing and risk assessment, e.g., linear no-threshold evaluations for genotoxic substances, evaluation of hazards/risks of complex mixtures, use of traditional Maximum Tolerated Dose approaches to both *in vitro* and *in vivo* testing?

4. What is required to assure a sound scientific process in applying the data appropriately for these two approaches? What are the differences? What areas may need greater attention where ICCA-LRI could contribute?

In the discussion, the participants considered both the opportunities and the obstacles presented by the new technologies. Discussion leaders provided short presentations on each of the questions in Exhibit 5 and then the participants worked together to synthesize some of the key issues raised during the discussions, which included priority setting, data transparency, and a critical concern surrounding understanding the data. The main points from these topics are summarized below.

- **Priority setting.** Because HTS allows for thousands of samples to be processed every day, a tendency to screen the entire universe of chemicals could exist. Because compound selection will be a critical step, it will be important to collaborate and coordinate across agencies and geographic boundaries to prioritize and make decisions about which compounds to test.

- **Data transparency.** If use of the new technologies are to successfully advance the risk assessment process, there must be appropriate data management systems in place so that data can be shared in its entirety. This is crucial for being able to interpret the data.
- **Understanding the data.** One of the challenges in collecting large volumes of data using technologies such as HTS is translating these data and understanding what they mean in the context of current data and for human health risk. There is a pressing need to understand the risk of the chemicals, not just their hazard. Toxicogenomics and other new technologies provide a tremendous opportunity but as the cost of testing is decreasing, the cost of interpretation is increasing and this should not be ignored.
    - **Contextual relevance.** The data collected using high-throughput analyses will need to be related to existing toxicology information using low-throughput methods. For conventional animal toxicity testing, the large amount of data that exists for well-studied compounds can provide a solid contextual framework. Existing data for well-studied compounds can be used to translate high-throughput assays into understood principles about how animals respond to these chemicals. However, it should be kept in mind that relevance not only applies to biological complexity but also to the question of dose. It will be important to test at doses that are relevant to human exposures because, mechanisms activated by high dose exposures are not likely the same as those for low, environmentally-relevant doses.
    - **Biological pathways.** High-throughput assays show us whether individual genes or proteins are affected when certain doses of chemicals are applied. Although subtle effects can be measured using high-throughput tests, it is not yet understood how these changes may relate to toxic responses in whole organisms. It will be important to translate the measured changes into what it means for toxicity, including understanding how the body responds and functions at different doses. It is also important to think beyond individual genes and more about integrated systems, considering how biological pathways may respond. In many regulations, safety factors are included to protect human health but are not always based on scientific data. The goal, as outlined in the recent NRC report (2007a), would be to conduct toxicity testing in human cells or cell lines *in vitro* by evaluating cellular responses in a suite of response pathway assays using high-throughput tests. Dose-response modeling of perturbations of pathway function would be organized around computational systems biology models of the circuitry underlying each response pathway. *In vitro* to *in vivo* extrapolations would rely on pharmacokinetic models that would predict human blood and tissue concentrations under specific exposure conditions.
    - **Human exposure.** In addition to understanding the biology, more attention to human exposure and what this means for predicting realistic risk to humans is needed. It will be important to understand the range and internal dose to which humans are exposed. This is especially critical when it comes to biomonitoring and understanding what measured chemical levels really mean in terms of risk.

Participants also noted that although much of the current focus is on toxicogenomics and other "omics" technologies, opportunities exist to use other technologies and to consider

technologies beyond "omics." These include nanotechnologies and micro-technologies, such as multi-electrode arrays, surface patterning and throughput image analysis.

3.3 Session 3: Risk Assessment

The primary focus of this session was how applications of new technologies in biomonitoring and toxicity testing can facilitate risk evaluations, public health decision making, and how to communicate results to the public, the media, and the medical community. The advanced technologies and how to appropriately interpret the large amounts of data that they can generate present both opportunities and challenges for risk assessment. The group discussed how to:

- Motivate a commitment to investing in the science to take advantage of the new methods/technologies
- Achieve contextual relevance of the voluminous quantities of data
- Invigorate the risk assessment community to modernize their framework and take advantage of these data
- Provide insights into data needs to render more value to the high-throughput data

Computational systems biology and strategies for toxicity testing

The first presentation of this symposium reviewed the role of computational systems biology in the NRC's vision for toxicity testing in the 21st century and recognized that the vision is easier said than done. Challenges include unknown metabolites, unknown response pathways, testing over ranges of doses, definition for a significant perturbation, and specific test methods. As assays are developed, information about systems will give rise to discovery of factors that augment the activity—biomarkers of sensitivity. Susceptibility will be informed by bioassays through expression of regulators. Circuitry model could be developed for all key assays to support dose-response assessment for observed responses, and genomics could be used for understanding response pathways.

The participants discussed what is meant by "computational" and "perturbation." Computational methods support interpretation and provide ways to organize and piece together what is known to identify outcomes. Perturbation means change and it constitutes the activation of toxicity. A response pathway is a cellular pathway that can be altered, perturbed, or changed. Eighteen key pathways have been identified *in vitro*. Definitions need to be developed and communicated to improve understanding of these terms outside of the United States. The NRC report discusses strategies for managing information and how the focus should be on transition and implementation. There will be a need for new tools to bridge the transition.

What about exposure?

One presentation challenged the session participants to think about whether the exposure components of the NRC panel's vision can be expanded. The NRC panel recommended that exposure should be addressed at each step, i.e. exposure needs to be considered along the way, not just at end; how this will be done remains to be determined. Exposure information can be

used to increase the efficiency of the testing process, help inform toxicity testing, describe risks, and verify outcomes of testing. Thus, it is important to progress from an exclusive toxicity-testing view to a public-health oriented perspective that includes consideration of exposure and prioritization of testing investments. When prioritizing chemicals for risk evaluation, screening approaches should include exposure and hazard; screening level exposure models should account for life cycle of intended product use, physical chemical properties, and transformation products. These data will be very important for chemicals with high reactivity in the environment, such as nanoparticles.

Biological consequences of a perturbation depend upon magnitude, timing, and duration of dose. Linked exposure/PBPK models will provide dose information that reflects the real-world and should provide the scientific base for dosing regimes. Toxicity testing with *in vitro* tests provides flexibility to evaluate real-world exposure scenarios, and sufficiently high doses to generate a response. Using a systems approach, this can be interpreted and accepted in a real world context by using different sources of data. Toxicity tests give us early indicators and indicators of effect, while other health studies give us markers of susceptibility. Exposure metrics are available (e.g., biomarkers, personal exposure samples). Population-based measurement studies with all three metrics demonstrate the linkages in real people at real exposure levels. Including these metrics in surveillance programs can be used to evaluate the impact of prospective decisions.

Exposure science can be moved forward by:

- Developing relational databases for characterizing exposure and dose – link to toxicity data, e.g., DSSTox (U.S. EPA 2008b) and ACToR (U.S. EPA 2008c).
- Refining and harmonizing screening-level models (e.g., QSAR and computational methods) for chemical prioritizations and screening-level assessments.
- Developing and linking models of source/concentration/exposure/dose, including linking across various scales; improving computational efficiency; and developing predictive methods for pharmacokinetic properties.
- Characterizing exposure processes and exposure factors using new approaches (e.g., informatics, network theory).
- Developing new methods and tools for conducting human exposure and surveillance studies.

These research needs are even more critical given that REACH legislation is driven by exposure. A major question is how low must exposures be in order to preclude testing.

One way to help communicate is the Exposure Prioritization Community of Practice (see (http://www.epa.gov/ncct/practice_community/exposure_science.html), an open-membership forum to share experience and begin the dialogue required to identify a path forward for exposure science for toxicity testing. The forum currently has approximately 40 members from government, industry, academia, environmental advocacy groups.

How can toxicogenomics improve risk assessment?

A second presentation described both examples and the challenges of for the use of toxicogenomics data in risk assessment using read-across and family approaches. These approaches are effective at predicting early events, but not outcomes. Challenges to using toxicogenomics in risk assessment include validation of technologies, development of tools for analyzing data, relating transcription products/metabolomics to toxicity, publicly-accessible databases, and applications in a regulatory context. The use of toxicogenomics also poses risk communication challenges because the methods generate markers of interaction, not effect and such results are difficult to explain.

Toxicogenomics can facilitate and accelerate classification and identification of mode of action for chemicals. The data can also assist in the design of effective and efficient testing strategies (e.g., reduce animal use, decrease length of tests). Toxicogenomics can enable measurement of exposure and effect in human epidemiological studies, and in the future, with the development of improved techniques, it may be used the way measurements of biochemical parameters are used today.

Several studies provide good examples for comparisons between the genomic biomarkers and conventional markers, including nephrotoxicity (Wang et al. 2008), immunotoxicity (Baken et al. 2008) and carcinogenicity (Ellinger-Ziegelbauer et al. 2004). Gene expression profiling has the potential to provide mode of action information (Fielden et al. 2007). Fielden et al. (2008) reviews results of data sharing to test the predictivity of two published hepatic gene expression signatures for non-genotoxic carcinogens (Fielden et al. 2007; Nie et al. 2006). Toxicogenomics analysis of short-term *in vivo* studies supports prediction of the carcinogenic potential of rat hepatocarcinogens. Mechanistic information is as an excellent predictor for distinction between genotoxic, non-genotoxic, and non-hepatocarcinogens. Mapping metabolite changes onto metabolic pathways also supports mechanistic understanding; proprietary software has been developed to support these analyses. “Metabolic profiling” may be useful for grouping substances.

The path to integration of advanced technologies in risk assessment: Developments, opportunities, and challenges

Another presentation reviewed the application of advanced technologies in risk assessment using the Canadian Environmental Protection Act as a case study and discussed international progress in training on mode of action approaches. The Canadian Environmental Protection Act requires assessments of Priority and Existing Substances. Simple and complex priority-setting tools are used for both hazard and exposure. Potential for exposure is influential in setting priorities. Quantitative or non-quantitative structure-activity relationships (QSARs or SARs) are used in prioritization and assessment. However, a need exists for transparent models for broader application for human health endpoints. The effort needs to involve risk assessors, endpoint specialists, and modellers. It needs to improve the capture of relevant data, and it needs to have more mode of action relevance for human health with emphasis on early events because most cancer or genotoxicity represent late toxicity endpoints.

Experience from Canada's categorization approach showed that it could draw significantly from profiles of substances with similar uses, properties, and hazards. There was early and continuing consideration of exposure (e.g., use profiling), of mode of action, and implications for dose-response. Moving away from default approaches to biologically-based approaches for dose-response assessment is an important aspect because it puts the assessment in the context of data that informs mode of action. It also enables clear identification of critical data gaps to reduce uncertainty, moves the focus to early key events, and promotes consistency. The approaches include categorical (categories of substances/species based on their characteristics (e.g., gases/particles)), chemical-specific adjustment factors that address kinetic or dynamic aspects with chemical- specific or compound-related information, and fully data-derived in which biologically-based dose-response modelling addressing kinetic and dynamic aspects.

The development of additional case studies on DNA reactive compounds, multiple modes of action (including "omics"), and training materials and outreach are needed. Formal extension of the mode of action frameworks to dose-response and co-exposures (i.e., mixtures); projects are being conducted on combined exposures to multiple chemicals. There is a need for planning and interface for effective uptake of the risk assessment community through communication and training.

Conclusions and Responses to Breakout Questions

To conclude this parallel symposium, a panel of discussion leaders initiated a group discussion on the questions presented in Exhibit 6. The questions focused on developing the path from data (the large volume of biomonitoring and testing results) to information (understanding what the data mean in the context of risk and informing the public health process) to decisions (implementing the gathered information in a risk assessment context). The purpose of these questions was to stimulate a discussion among the members of this symposium so that progress can continue to be made in terms of how applications of new technologies in biomonitoring and toxicity testing can assist in public health decision making and in communicating results.

Exhibit 6
Symposia Session 3 Questions: Risk Assessment

1. Can the existing risk assessment framework take advantage of the data offered by new technologies?
2. How can we invigorate the risk assessment community to modernize their framework and develop innovative tools to take advantage of these data?
3. From a regulatory perspective, how do these data enable us to protect individuals, specifically those who are susceptible?
4. As the technology advances, what are the considerations when developing individual risk profiles become possible?
5. How do we ensure that a holistic systems approach is considered so that the data are not judged out of context?

Can the existing risk assessment framework take advantage of the data offered by new technologies?

Participants believed that although the existing framework can take advantage of the data from the new technologies, a better understanding of what they mean and how they are interpreted is needed. A general concern was about the misinterpretation of traditional endpoints. Because they could be taken out of context, participants believed that it will be to anchor the results to phenotypic response. The new available information may not as helpful for those chemicals that have human data, but it would be useful for chemicals without these data. A framework for communication stewardship and how information is communicated responsibly is also needed.

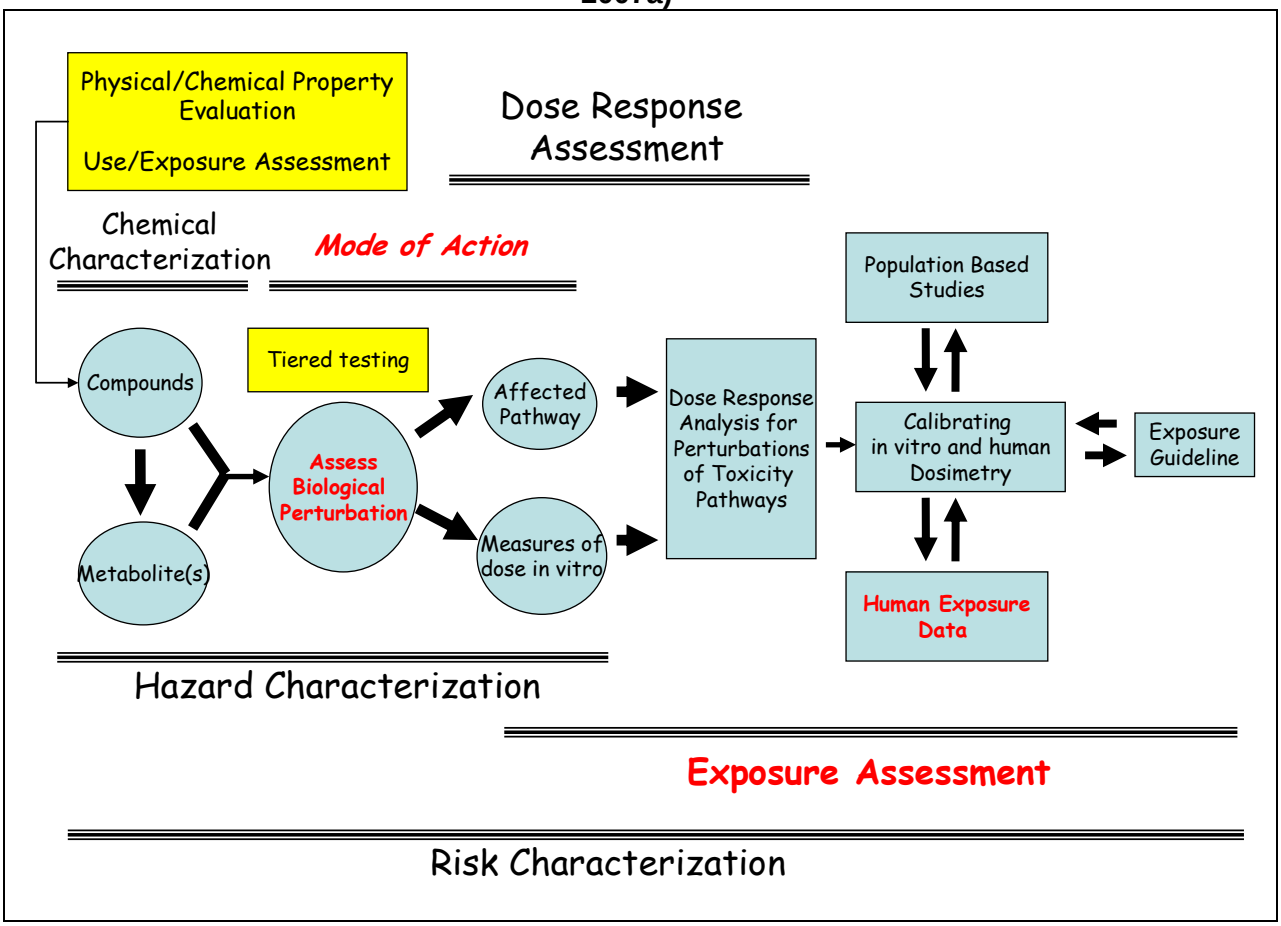
How can we invigorate the risk assessment community to modernize their framework and develop innovative tools to take advantage of these data?

Efforts to invigorate the risk assessment community to embrace the new technologies can be led by a few agents of change as well as current support for modernization of risk assessment. Regulatory-driven needs to address large numbers of substances, and the new technologies should be utilized to address these needs. Because more work will need to be done with fewer resources, costly and time-consuming single-chemical risk assessments should become a thing of the past. Compound categories, mode of action information and exposure data will all be necessary for accurate grouping of chemicals.

The group suggested that NRC framework is missing a tiered exposure evaluation as a starting point. In such a tiered testing scheme, the exposure and hazard interconnect more directly earlier on in the process. The approach would look at chemical structure, use, and background exposure levels before testing. These evaluations can provide information about kinetics and support preliminary modeling or kinetic testing. In some cases, it may be determined

that a particular chemical might not ever get into the body or the environment. Investments in metrics of exposure will also be needed to support the systems approach.

Exhibit 7
Include exposure considerations (chemical/physical properties, uses, and kinetics) in the chemical characterization phase and establish tiered testing schemes (NRC 2007a)



There needs to be targeted testing to cover the chemical space, which includes various chemical classes with different chemical characteristics. Many PBPK models relate to the volatile organics, but are less applicable for lipophilic compounds.

Scientists and regulators need to be trained in the new technologies, and risk assessors, risk managers, first-line managers, and senior managers need to be educated. They need to know that the mode of action frameworks and case studies are available. An active scientific community needs to convince risk assessors to move away from use of uncertainty factors. These frameworks can help to delineate the types of data that are preferred over defaults, support moving towards a mechanistic approach, and insure that risk assessment is an appropriate tool or at least answering the right question. Effective communication will be needed to inform the general public informed and improve science education.

The changes need to be communicated in a familiar context, such as chemical-specific adjustment factors. The communication efforts should also include the value and benefits of using the frameworks, technology, and data need to be proven. The myth that using a default approach is always protective needs to be challenged. We need to identify what is needed to convince people that within the existing framework and in the broader community, we can move to a new mode of action-centered process.

A definition of what constitutes a significant perturbation is needed because different perceptions currently exist. Linkages and system approaches to understand range of normal (i.e., what is homeostasis) will be required to understand the tipping point. We can begin to use this information with these frameworks but only with phenotypic anchoring to the existing toxicity data.

From a regulatory perspective, how do these data enable us to protect individuals, especially those who are susceptible? As the technology advances, what are the considerations when developing individual risk profiles?

The group noted that at an individual level, there are improved measures of individual etiological processes and individual exposures (e.g., genetic profiling, personal biomonitoring) that may eventually translate into a personal risk profile. But the challenge is what to do with that information. The concern is that a lot of information is out there, but most of it is not interpretable. The challenge will be to make the information useful for medical providers and those individuals who can make choices based on a better understanding of personal risks. At a population level, there are ways to identify genetic variants and identify susceptibility. It was noted that epigenetic modification could impact genetic variability.

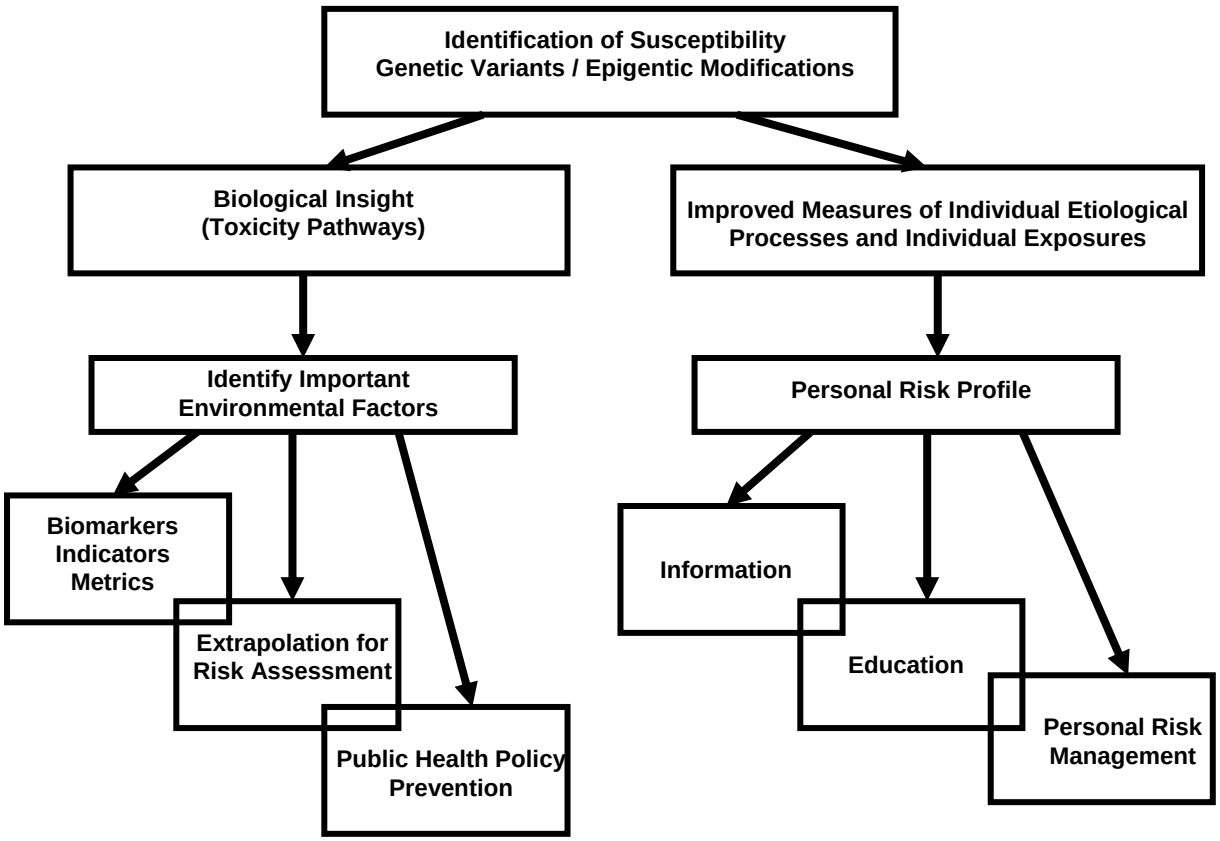
The challenges are dynamic and risks for chemicals must be evaluated with a focus on addressing those risks with the greatest potential impact. Approaches should be holistic and consider that many lifestyle risk factors exist.

The group encouraged establishing metrics now for systems biology and to help move risk assessment forward into the process. Ensuring key measurements in the mode of action realm will better position a move towards a holistic understanding.

Exposure assessment is just as important, but its current status is 20 to 30 years behind toxicity testing. Funding is needed to develop a mechanistic model for exposure assessment. Funding for exposure assessment research needs to be more commensurate with toxicity testing expenditures.

An understanding of personal susceptibilities for disease can inform choices about acceptable risks. However, more work on human disease states and toxicity pathways leading to the disease states is needed. For most complex traits, the disease variants identified to date explain only a small proportion of individual variation in risks for disease. For most individuals, genetic profiling based on the currently available markers provides only limited information on risk beyond that of conventional risk factors.

Exhibit 8
Framework for Translating Susceptibility for Risk Management
(Dr. Elaine Cohen-Hubal's presentation; see also McCarthy et al. 2008)



4.0 LOOKING AHEAD: THE PATH FORWARD FOR TWENTY-FIRST CENTURY APPROACHES TO TOXICITY TESTING, BIOMONITORING, AND RISK ASSESSMENT

The final plenary session focused on the path forward; specifically, it focused on how the information presented during the plenary sessions and the ideas discussed during the parallel symposia sessions (described in Section 3.0) can be advanced. Presentations in this final session included approaches for practical application and translation of biomonitoring data into policy. These presentations focused not only on how to move from identifying hazards to identifying risks but also how to move from population risk to individual risk. To make informed risk assessment decisions, investigators must design and conduct studies that will improve our understanding of response pathways, dose response, low dose effects, and polymorphisms.

Understanding mode of action for chemicals will be essential and will require knowledge of biological systems and expert judgment, as well as time and monetary investments. Response pathways can be identified through a combination of *in vivo* studies with animal models to develop comprehensive toxicity maps and *in vitro* tests with human cells. As a result, the cost of data generation will decrease while the cost of data interpretation will increase. In order to effectively employ this approach, investigators must truly understand the relationships between *in vitro* doses and *in vivo* effects.

Current trends in risk assessment indicate a shift towards innovations that can improve the method and include a focus on mode of action and human pathway approaches. Additional stakeholder collaboration and new technology developments will be necessary for success. Technology can make a difference in hazard evaluation related to the relevance of data to humans, the separation of adaptive responses from adverse reactions, the relationship between the adverse response and the mechanism of toxicity, and mechanistic studies that separate qualitative differences between species from quantitative, as well as change the way risk assessment is applied.

Once new techniques have been developed and data have been collected and analyzed, the next step is to translate risk data into effective policy decisions. As stated previously, communication among all stakeholders, including the public, is essential because public perception is a critical driver for policy development. With the anticipated influx of new risk and hazard data, policy-makers must be aware of the public's perception of risk, the threat of misinformation, and the possibility of false positives. Policy-makers can learn from success stories on how science affected policy (e.g., lead, mercury), as well as issues that have been uncovered by science and not addressed by policy (e.g., endocrine-related cancers). These case studies have shown that public perception can largely influence policymaking.

The workshop was viewed as a success because it helped to initiate essential discussions regarding the use of the new technological advances to improve risk assessment. The specific aims achieved included highlighting chemical industry engagement, activities and impact and promoting discussions of future work among a variety of interested parties. The ICCA-LRI workshop provided an opportunity to highlight the chemical industry's role as a leader not only for human biomonitoring research but also for research to implement the new technologies. Another success from the workshop was obtaining feedback and input from academics, regulators, and government representatives to identify knowledge gaps and to define research directions for use of the new technologies. The workshop allowed participants to initiate discussions of the scientific basis for policies, how these new technologies could play a role in risk assessment, and how to build consensus among stakeholders to modernize risk assessment. Lastly, the workshop improved understanding of the impact of complex environments on health; this aim was achieved through discussion of case studies that use the new technologies and criteria for data interpretation. The future direction of the ICCA-LRI will be informed by the lessons learned from the workshop to improve the current risk assessment paradigm.

5.0 REFERENCES

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APPENDIX A: ICCA-LRI 2008 WORKSHOP AFFILIATIONS OF PARTICIPANTS

American Chemistry Council
Arcadis Belgium, nv
Arch Chemicals, Inc.
AstraZeneca
BASF SE
Bayer AG
Bayer CropScience AG
Bayer HealthCare AG
Bayer MaterialScience
Beiersdorf AG
BGFA – Research Institute of Occupational Medicine
BioDetection Systems BV
Canadian Chemical Producers' Association
Cefic (European chemical industry council)
Centers for Disease Control and Prevention
Center of Public Research – Gabriel Lippmann
Central Science Laboratory
Chemical Industries Association
Ciba Inc.
CNRS MNHN
CONCAWE
Connecticut Department of Public Health
Cranfield University
Currenta
Dow Chemical Company
Dow Corning Corporation
DSM
DuPont Coordination Center
DuPont Engineering
Ecobaby Foundation
ENVIRON International Corporation
Euro Chlor
European Centre for Ecotoxicology and Toxicology of Chemicals
European Commission, DG Joint Research Centre
EVMTech
Ewha Womans University
Expert Centre for Substances
Exponent
ExxonMobil Petroluem and Chemical
Federal Insititute for Risk Asessment
Federchimica
General Health Directorate
German Academy of Pediatrics
Health and Safety Laboratory, UK
Health Protection Agency, UK
Human Society of the United States
ICF International
ICIS
Imperial College London, Hammersmith Campus
Imperial Oil Limited
Imperial Tobacco
IndusTox Consult
IndusTox Consult
Institute of Public Helath Timisoara
Instituto de Salud Carlos III
International Flavors & Fragrances Inc.
Japan Chemical Industry Association
Johnson and Johnson
JohnsonDiversey International
Korea Food and Drug Administration
Laboratory for Health Protection Research
Lion Corporation
LyondellBasell Industries
Maastricht University
Medical Research Council
Momentive Performance Materials
National Institute for Environmental Studies, Japan
National Institute of Health, USA
National Institute of Public Health and the Environment (RIVM),
The Netherlands
National Institute of Toxicological Research, Korea
Procter and Gamble
Robert Koch Institute
RWTH Aachen
Shell International BV
Showa Pharamaceutical University
Solvay
Sumitomo Chemical Company, Ltd.
Summit Toxicology
Syngenta
The Hamner Institutes for Health Sciences
TNO - Quality of Life
Umweltbundesamt
Unilever Research
United States Environmental Protection Agency
United States Government Accountability Office
University of Aarhus
University of Amsterdam
University of Erlangen-Nuremberg
University of Manchester
University of Ottawa
Verband der Chemischen Industrie (VCI)
VITO (Flemish Institute for Technological Research)
WatchFrog
Watts & Crane Associates
WHO/IPCS Inter-Regional Research Unit

APPENDIX B: ICCA-LRI 2008 WORKSHOP FINAL AGENDA

Workshop Chair:
Richard Phillips, ExxonMobil

Monday, June 16, 2008

07.00 – 08.00	**Registration and Continental Breakfast**
08.00 – 08.50	*Session Chair:* **Richard Phillips**, ExxonMobil, Belgium Welcome • **David Duncan**, Unilever, UK, on behalf of the Cefic Research & Innovation Programme Council • **Antonio Lacerda de Queiroz**, European Commission, Belgium
08.50 – 09.00	Workshop objectives and expectation of outcome • **Richard Phillips**, ExxonMobil, Belgium

Plenary Session I: The Context

09.00 – 10.00	*Session Chair:* **Marc Willuhn**, Cefic (European Chemical Industry Council), Belgium *Speakers:* (30 minutes each, including Q&A) Dealing sensibly with environmental health risks in the 21st century • **Erik Lebret**, The National Institute for Public Health and the Environment (RIVM), The Netherlands Toxicity testing in the 21st century: A vision and a strategy • **Daniel Krewski**, University of Ottawa, Canada
10.00 – 10.30	**Morning Break**

Plenary Session II: Setting the Stage for the Parallel Symposia

10.30 – 12.30

Session Chair: **Tina Bahadori**, American Chemistry Council, USA

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

Public health opportunities of human biomonitoring within an evolving risk framework

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

Omics-based biomarkers for chemical safety: An overview of EU efforts

- **Jos Kleinjans**, University of Maastricht, The Netherlands

ToxCast™: One step in fulfilling the NRC's vision of toxicity testing in the 21st century

- **Robert Kavlock**, Environmental Protection Agency, USA

Heavy metal and tobacco smoke toxicity and individual genetic susceptibility

- **Karl Ernst von Muehlendahl**, Children's Hospital in Osnabrück, Germany

12.30 – 14.00 **Lunch**

Parallel Symposium Sessions

14.00 – 17.00

(including a 30 min **Afternoon Break**)

Session 1: Human Biomonitoring

Chair: **Ulrike Zimmer**, VCI (German chemical industry association), Germany
Rapporteur: **Herman Autrup**, University of Aarhus, Denmark
Recorder: **Ami Parekh**, ICF International, USA

Description of parallel symposia and charge to participants (15 minutes)

- **Ulrike Zimmer**, VCI (German chemical industry association), Germany

Speakers: (15 minutes each for the first two, 30 minutes each for the second two, with 45 minutes for discussion and Q&A)

The concept and results of the German health interview and examination survey for children and adolescents (KiGGS)

- **Bärbel-Maria Kurth**, Robert Koch Institute, Germany

The German environmental survey on children: Exposure of children to environmental factors

- **Marike Kolossa-Gehring**, Federal Environment Agency, Germany

Temporal trends in general population-based exposures

- **Dana Barr**, Centers for Disease Control and Prevention, USA

The German Human Biomonitoring Commission

- **Juergen Angerer**, University of Erlangen-Nuremberg, Germany

14.00 – 17.00 (including a 30 min **Afternoon Break**)	Session 2: Advanced Technologies *Chair:* **David Dix**, Environmental Protection Agency, USA *Rapporteur:* **James Bus**, Dow Chemical Company, USA *Recorder*: **Rebecca Kauffman**, ICF International, Sweden Description of parallel symposia and charge to participants (15 minutes) • **David Dix**, Environmental Protection Agency, USA *Speakers:* (30 minutes each with 15 minutes for discussion and Q&A) Quantitative high-throughput screening of the Tox21 compound collection • **Christopher Austin**, National Institutes of Health, USA The EU-FP6 PredTox project: Using an integrated "omics" approach to mechanistic biomarker identification • **Heidrun Ellinger-Ziegelbauer**, Bayer HealthCare AG, Germany Toxicogenomics to improve prediction and risk assessment • **George Daston**, Procter & Gamble, USA The analysis of genomic dose-response data to define mode-of-action and low-dose behavior of chemical toxicants • **Russell Thomas**, The Hamner Institutes for Health Sciences, USA
14.00 – 17.00 (including a 30 min **Afternoon Break**)	Session 3: Risk Assessment *Chair:* **Richard Becker**, American Chemistry Council, USA *Rapporteur:* **Kathleen Plotzke**, Dow Corning Corporation, USA *Recorder*: **Kimberly Osborn**, ICF International, USA Description of parallel symposia and charge to participants (15 minutes) • **Richard Becker**, American Chemistry Council, USA *Speakers:* (30 minutes each with 45 minutes for discussion and Q&A) Computational systems biology and strategies for toxicity testing in the 21st century • **Melvin Andersen**, The Hamner Institutes for Health Sciences, USA What about exposure? • **Linda Sheldon**, Environmental Protection Agency, USA How may toxicogenomics improve risk assessment? • **Ursula Gundert-Remy**, Federal Institute for Risk Assessment, Germany
17.00 – 18.00	**Break and Aperitif**
18.00 – 19.00	**Reception and Poster Viewing**
19.00 – 21.00	**Group Dinner**

Tuesday, June 17, 2008

07.00 – 08.00	**Continental Breakfast**

Parallel Symposium Sessions / Panel Discussions

08.00 – 10.00 Session 1: Human Biomonitoring

Chair: **Ulrike Zimmer**, VCI, Germany
Rapporteur: **Herman Autrup**, University of Aarhus, Denmark
Recorder: **Ami Parekh**, ICF International, USA

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

Working backwards: Estimating exposure and risk from human biomonitoring data

- **Harvey Clewell**, The Hamner Institutes for Health Sciences, USA

Biomonitoring equivalents: Lessons learned and current status

- **Sean Hays**, Summit Toxicology, USA

Panel discussion (5-10 minute set-up by discussion leader listed below and then 10 minute group discussion for each question)

Discussion Leaders:

- **Ovnair Sepai**, Health Protection Agency, UK
- **Greet Schoeters**, Flemish Institute for Technological Research, Belgium
- **Peter Boogaard**, Shell International, The Netherlands

08.00 – 10.00 Session 2: Advanced Technologies

Chair: **David Dix**, Environmental Protection Agency, USA
Rapporteur: **James Bus**, Dow Chemical Company, USA
Recorder: **Rebecca Kauffman**, ICF International, Sweden

Panel discussion (5-10 minute set-up by discussion leader listed below and then 15-20 minute group discussion for each question)

Discussion Leaders:

- **Remi Bars**, Bayer CropScience, France
- **Timothy Gant**, University of Leicester, UK
- **Sandra Coecke**, European Commission Joint Research Center, Italy
- **James Bus**, Dow Chemical Company, USA
- **Melvin Andersen**, The Hamner Institutes for Health Sciences, USA

Parallel Symposium Sessions / Panel Discussions (continued)

08.00 – 10.00

Session 3: Risk Assessment

Chair: **Richard Becker**, American Chemistry Council, USA
Rapporteur: **Kathleen Plotzke**, Dow Corning Corporation, USA
Recorder: **Kimberly Osborn**, ICF International, USA

Speaker: (30 minutes including Q&A)

The path to integration of advanced technologies in risk assessment: Developments, opportunities and challenges

- **Bette Meek**, University of Ottawa, Canada

Panel discussion (5-10 minute set-up by discussion leader listed below and then 15-20 minute group discussion for each question)

Discussion Leaders:

- **Gerard Swaen**, The Dow Chemical Company, The Netherlands
- **Bette Meek**, University of Ottawa, Canada
- **Richard Becker**, American Chemistry Council, U.S
- **Elaine Cohen-Hubal**, Environmental Protection Agency, USA

10.00 – 10.30 **Morning Break**

Parallel Symposia Report Back

10.30 – 12.30

*Chai*r: **Janet Mostowy**, Bayer MaterialScience, USA

Speakers: (30 minutes each, followed by discussion of interdisciplinary issues and Q&A)

- **Herman Autrup**, University of Aarhus, Denmark
- **James Bus**, Dow Chemical Company, USA
- **Kathleen Plotzke**, Dow Corning Corporation, USA

12.30 – 14.00 **Lunch**

Plenary Session III: Looking Ahead

14.00 – 15.20	*Chair:* **Timothy Gant**, University of Leicester, UK Workshop outcomes and path ahead • **Timothy Gant**, University of Leicester, UK *Speakers:* (30 minutes each, including Q&A) Risk assessment: A practical perspective • **Lewis Smith**, Syngenta, UK From data to policymaking • **Peter Pärt**, European Commission Joint Research Centre, Italy
15.20 – 15.30	Workshop conclusions • **Richard Phillips**, ExxonMobil, Belgium
15.30 – 16.00	**Afternoon Break**

APPENDIX C: ICCA–LRI 2008 WORKSHOP
LIST OF POSTER PRESENTATIONS

	First Author ***Affiliation***	**Presenter** ***Affiliation***	**Abstract Title**
1	R. Bevan *Cranfield University, UK*	R. Bevan *Cranfield University, UK*	The UK Interdepartmental Group on Health Risks from Chemicals: Past achievements and future aims
2	J. Cocker *Health & Safety Laboratory, UK*	K. Jones *Health & Safety Laboratory, UK*	Background incidence of key biomarkers of chemical exposure within the general UK population
3	E. Den Hond *VITO (Flemish Institute for Technological Research), Belgium*	G. Schoeters *VITO (Flemish Institute for Technological Research), Belgium*	Inter-individual variation in key biomarkers within the general population
4	E. Den Hond *VITO (Flemish Institute for Technological Research), Belgium*	G. Schoeters *VITO (Flemish Institute for Technological Research), Belgium*	Inter-individual variability of three persistent biomarkers in three age classes
5	E. Fritsche *Environmental Health Research Institute, Germany*	E. Fritsche *Environmental Health Research Institute, Germany*	Human neurospheres identify threats for brain development
6	M. Gödde *Helmholtz Research Center, Germany*	U. Zimmer *VCI (German Chemical Industry Association), Germany*	Human-Biomonitoring Information Service: Interface between science, authorities and public
7	E. Govarts *VITO (Flemish Institute for Technological Research), Belgium*	G. Schoeters *VITO (Flemish Institute for Technological Research), Belgium*	Determinants of serum PCBs in adolescents and adults: Linear regression analysis and regression tree analysis
8	D. Huizer *Industox, The Netherlands*	D. Huizer *Industox, The Netherlands*	Development of a computational multi-level modelling tool for the estimation of biomonitoring equivalent guidance values for chemical agents related to health based exposure rates for inhalation, oral intake and/or skin exposure
9	M. Hwang *Korea Food and Drug Administration, Korea*	M. Hwang *Korea Food and Drug Administration, Korea*	Application of toxicogenomic technology for the improvement of risk assessment
10	J. Koppe *University of Amsterdam, Netherlands*	J. Koppe *University of Amsterdam, Netherlands*	Human biomonitoring and the baby: No place for cord blood
11	W.S. Lee *Korean Food and Drug Association, Korea*	W.S. Lee *Korean Food and Drug Association, Korea*	Prediction of carcinogenicity *in vitro* based on genotoxicity, toxicogenomics data and statistical approaches including LogitBoost

	First Author *Affiliation*	Presenter *Affiliation*	Abstract Title
12	M. Leijs *University of Amsterdam, Netherlands*	M. Leijs *University of Amsterdam, Netherlands*	Human biomonitoring of dioxins in breastmilk and research
13	G. Leng *Biomonitoring Institute of Currenta, Germany*	G. Leng *Biomonitoring Institute of Currenta, Germany*	Human biomonitoring and risk communication
14	A. Povey *Manchester University, UK*	A. Povey *Manchester University, UK*	Toxicity induced by DNA damaging agents in DNA glycosylase proficient and deficient mouse fibroblasts lacking additional DNA response genes
15	H. Sone *National Institute for Environmental Studies*	J. Yonemoto *National Institute for Environmental Studies*	A genome informatics and epidemiological study identifies alleles in AHR responsive genes associated with risk of male genital organ disorders
16	E. Tielemans *TNO Quality of Life, The Netherlands*	E. Tielemans *TNO Quality of Life, The Netherlands*	Development of an advanced exposure assessment tool for REACH
17	K. Travis *Syngenta, UK*	G. Swaen *The Dow Chemical Company, The Netherlands*	A framework for the integration of human and animal data in chemical risk assessment
18	D. van Leeuwen *Maastricht University, The Netherlands*	D. van Leeuwen *Maastricht University, The Netherlands*	Transcriptome analysis in peripheral blood of humans exposed to environmental carcinogens: A promising new biomarker in environmental health studies
19	H. Yamazaki *Showa Pharmaceutical University, Japan*	H. Yamazaki *Showa Pharmaceutical University, Japan*	Challenges for precision of risk evaluation systems in Japan: From chemical doses for animals to their concentrations in human bodies
20	D-Y. Yoon *Konkuk University, Korea*	D-Y. Yoon *Konkuk University, Korea*	Profiling analyses of transcripts and proteins modulated by E7 oncogene in the lung tissues of E7 Tg mouse by omics approaches