



# Integrating New Advances in Exposure Science and Toxicity Testing: Next Steps

## Workshop Summary Report

**16-17 June 2010**

**Grand Hotel Bristol**

Stresa, Italy



INTERNATIONAL  
COUNCIL OF  
CHEMICAL  
ASSOCIATIONS



## Contents

Organizing Committee Members.....	i
List of Acronyms.....	iii
About the ICCA-LRI .....	iv
Executive Summary.....	v
1.0 Introduction .....	1
2.0 Welcome Remarks .....	1
2.1 Plenary Session I – Integrating Science for Chemical Safety Assessment .....	2
2.2 Plenary Session II – Setting the Stage for the Breakout Sessions .....	4
3.0 Breakout Sessions.....	7
3.1 Breakout Session 1 - <i>Exposure Science</i> .....	7
3.2 Breakout Session 2 – <i>Toxicity Testing</i> .....	13
3.3 Breakout Session 3 – <i>Communicating Scientific Information</i> .....	19
4.0 Plenary Session III – Actualizing Innovation .....	25
5.0 Workshop Summary .....	27
References .....	29
Appendix A: Participant Affiliations.....	A-1
Appendix B: Workshop Program .....	B-1
Appendix C: List of Poster Presentations .....	C-1



## Organizing Committee Members

**Annette Guiseppi-Elie, Co-Chair**

DuPont  
Charlotte, NC, United States  
[annette.guiseppi-elie@usa.dupont.com](mailto:annette.guiseppi-elie@usa.dupont.com)

**Maurice Whelan, Co-Chair**

Institute for Health and Consumer Protection,  
Joint Research Centre, European Commission  
Ispra, Italy  
[maurice.whelan@ec.europa.eu](mailto:maurice.whelan@ec.europa.eu)

**Herman Autrup**

University of Aarhus  
Aarhus, Denmark  
[ha@mil.au.dk](mailto:ha@mil.au.dk)

**Tina Bahadori**

U.S. Long-Range Research Initiative (LRI),  
American Chemistry Council  
Arlington, VA, United States  
[tina\\_bahadori@americanchemistry.com](mailto:tina_bahadori@americanchemistry.com)

**Brenda Barry**

U.S. LRI, American Chemistry Council  
Arlington, VA, United States  
[brenda\\_barry@americanchemistry.com](mailto:brenda_barry@americanchemistry.com)

**Melanie Bausen**

BASF - The Chemical Company  
Ludwigshafen, Germany  
[melanie.bausen@basf.com](mailto:melanie.bausen@basf.com)

**Elaine Cohen Hubal**

National Center for Computational Toxicology,  
U.S. Environmental Protection Agency  
Research Triangle Park, NC, United States  
[hubal.elaine@epa.gov](mailto:hubal.elaine@epa.gov)

**Lynn Frewer**

University of Wageningen  
Wageningen, Netherlands  
[lynn.frewer@wur.nl](mailto:lynn.frewer@wur.nl)

**Akira Fukushima**

Lion Corporation and  
Japan Chemical Industry Association (JCIA)  
Tokyo, Japan  
[af2@lion.co.jp](mailto:af2@lion.co.jp)

**Timothy Gant**

University of Leicester  
Medical Research Council  
Leicester, United Kingdom  
[twg1@leicester.ac.uk](mailto:twg1@leicester.ac.uk)

**Peggy Geimer**

Arch Chemicals, Inc.  
Norwalk, CT, United States  
[pngheimer@archchemicals.com](mailto:pngeimer@archchemicals.com)

**Loredana Guinea**

CEFIC aisbl (European Chemical Industry  
Council)  
Brussels, Belgium  
[lgh@cefic.be](mailto:lgh@cefic.be)

**Bruno Hubesch**

Long-Range Research Initiative, Research &  
Innovation, CEFIC aisbl  
Brussels, Belgium  
[bhu@cefic.be](mailto:bhu@cefic.be)

**Matti Jantunen**

National Institute for Health and Welfare  
Kuopio, Finland  
[matti.jantunen@thl.fi](mailto:matti.jantunen@thl.fi)

**Ian Kimber**

Faculty of Life Sciences, University of  
Manchester  
Manchester, United Kingdom  
[ian.kimber@manchester.ac.uk](mailto:ian.kimber@manchester.ac.uk)



**Masatoshi Kumamoto**

Chemicals Management Department,  
Japan Chemical Industry Association (JCIA)  
Tokyo, Japan  
[mkumamoto@jcia-net.or.jp](mailto:mkumamoto@jcia-net.or.jp)

**Janet Mostowy**

Bayer Corporation  
Pittsburgh, PA, United States  
[janet.mostowy@bayerbms.com](mailto:janet.mostowy@bayerbms.com)

**Grace Patlewicz**

DuPont  
Newark, DE, United States  
[grace.y.tier@usa.dupont.com](mailto:grace.y.tier@usa.dupont.com)

**Richard Phillips**

ExxonMobil Petroleum & Chemical  
Machelen, Belgium  
[richard.d.phillips@exxonmobil.com](mailto:richard.d.phillips@exxonmobil.com)

**David Rouquié**

Bayer Crop Science  
Sophia Antipolis, France  
[david.rouquie@bayercropscience.com](mailto:david.rouquie@bayercropscience.com)

**Gary Shrum**

Eastman Chemical Company  
Kingsport, TN, United States  
[glshrum@eastman.com](mailto:glshrum@eastman.com)

**Corinna Weinz**

Bayer AG  
Leverkusen, Germany  
[corinna.weinz@bayer.com](mailto:corinna.weinz@bayer.com)

**Andrew Worth**

Institute for Health and Consumer Protection,  
Joint Research Centre, European Commission  
Ispra, Italy  
[andrew.worth@ec.europa.eu](mailto:andrew.worth@ec.europa.eu)



## List of Acronyms

ACC	American Chemistry Council
ACToR	Aggregated Computational Toxicology Resource
Cefic	European Chemical Industry Council
COMET	Consortium for Metabonomic Toxicology
COPHES	Corsortium to Perform Human Biomonitoring on the European Scale
CRAFT	chemical reactivity and fate tool
CVST	Chemical Screening Visualization Tool
DART	decision analysis by ranking techniques
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EC	European Commission
EU	European Union
GerEs	German Environmental Surveys
G x E	genetic and environmental
hESC	human embryonic stem cell
HSDB	Hazardous Substances Database
hPSC	human pluripotent stem cells
ICCA	International Council of Chemical Associations
ITER	International Toxicity Estimates for Risk Assessment
ITS	integrated testing strategy
JCIA	Japan Chemical Industry Association
JRC	Joint Research Centre
LCMS	Liquid chromatography/mass spectrometry
Log Kow	logarithm of the octanol/water partition coefficient
LRI	Long-Range Research Initiative
METIS	METanomics Information System
MOA	mode of action
NCCT	National Center for Computational Toxicology
NLM	National Library of Medicine
NM	nanomaterial
NMR	nuclear magnetic resonance
NRC	National Research Council
OECD	Organisation for Economic Co-operation and Development
PBPK	physiologically-based pharmacokinetic
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
(Q)SAR	(quantitative) structure-activity relationship
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
SICM	scanning ion conductance microscopy
TOXNET	Toxicology Data Network
ToxPi	Toxicological Priority Index
UBA	Federal Environmental Agency in Germany
U.S. EPA	U.S. Environmental Protection Agency
VOI	Value of information



## About the ICCA-LRI

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

ICCA-LRI projects are implemented in cooperation with the scientific community and governmental institutions and the results are published and shared freely with the public, regulators, industry, and the academic and governmental communities. For this reason, the ICCA-LRI has developed research and communication strategies that link with outreach activities to governments, non-governmental organizations, and the public. A key component of the communication and outreach strategies has been a series of public workshops (see Figure 1) that focused on integrating the challenges of biomonitoring with broader issues such as toxicity testing, exposure assessment, and new methodologies for risk assessment. The goals for the workshops are designed to complement ongoing research, ensure coordination in implementation of regional ICCA-LRI research programs, continue engagement with public authorities, and provide leadership to others working in the research field. An LRI Beacon, *ICCA-LRI Workshops: Better Information for Better Decisions*, that provides additional information about the previous workshops listed in Figure 1 can be accessed at <http://www.icca-chem.org/lri>.

### Figure 1. Overview of ICCA-LRI Workshops

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

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

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

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

**2009 - Connecting Innovations in Biological, Exposure and Risk Sciences: Better Information for Better Decisions - Charleston, South Carolina, USA.** Focused on approaches to interpret the data from the new technologies and to advance risk-based decision-making; reviewed innovative tools to characterize exposure and the implications for health risk assessment; addressed the key role of communication to effectively explain the emerging research outcomes to diverse audiences.

## Executive Summary

The International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI), in conjunction with the European Commission's Joint Research Centre (JRC) held its 2010 Workshop, *Integrating New Advances in Exposure Science and Toxicity Testing: Next Steps*, on 16 and 17 June 2010 in Stresa, Italy. More than 120 participants from government, academia, non-governmental organizations, and industry representing 19 different countries attended the workshop, the sixth in the ICCA-LRI annual series.

Integrating developments in exposure science and toxicology is essential for meaningful advancement of knowledge-based decision making about the safety of chemicals. A key consideration for this workshop was application of integrated approaches in these scientific disciplines to the design, evaluation, and health risk management of chemicals. This workshop also considered what research is needed to improve communication between scientists and decision makers, and with stakeholders and end-users, including the public, to develop better chemical management policies and practices.

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



Workshop plenary session.

- Advances in molecular technologies are enabling environmental epidemiology and toxicology to identify the exposure-effect relationship at the cellular, organismal, and population levels.
- The success of these approaches hinges on the availability of biologically-relevant exposure information that is rapidly evolving from improved measurement technologies, more targeted biomonitoring studies, and applications of advanced informatics and computational tools.
- The exposome, defined as a lifetime of human environmental exposures including lifestyle factors, was highlighted as a possible framework for guiding developments in exposure science.
- Stem cells offer great potential for the development of *in vitro* toxicity models that are relevant to effects that can occur in humans; similarly, new imaging methods offer innovative approaches to understand mechanisms of toxicity in *in vitro* models.
- Computational models are becoming increasingly sophisticated and advanced both in the analysis of 'omics' data, such as high throughput methods, as well as in their predictive capabilities, such as for biological system interactions and (quantitative) structure- activity relationship [(Q)SAR] modeling.
- New informational tools, including the Toxicological Priority Index (ToxPi) and the Chemical Screening Visualization Tool (CVST), can incorporate and transform multiple types of chemical



information into visual formats that facilitate chemical prioritization and identification of areas for additional toxicity testing.

- Value of information (VOI) methods and other decision analysis tools provide an approach for identifying those test protocols that offer the best value in terms of resource allocation.
- Effective communication about chemicals must include both risk and benefit information so that all shareholders, including the public, are fully informed.
- Risk characterization is an analytical, deliberative, and decision-driven process; successful characterization of risk for chemicals requires getting the science and the participation right as well as getting the right science and the right participation.
- Stakeholders must be part of the risk assessment process to improve credibility and the utility of the results; input, dialogue, and engagement are more important than consensus among all stakeholders.

Undoubtedly, new cellular, analytical, and computational methods, alone and in combination, provide exciting new approaches for chemical evaluation and integrated testing strategies. However, a significant confluence of will and resources will be required to implement these strategies and to create the requisite paradigm shift in chemical safety assessments. Without a collective commitment to build capacity and to create a strategic shift, the advancements in science discussed at this workshop are likely to outpace the decision making, regulatory and policy mechanisms that need to adopt the new science.



Workshop participant asks a question during the plenary session.

This JRC & ICCA-LRI workshop provided an international forum to foster interactions among researchers and stakeholders, stimulate discussions for

improving the scientific basis for policy making, and support consensus building that can advance the risk assessment process for chemicals. This and the previous ICCA-LRI workshops demonstrate the value of participatory and collaborative development of the science relevant to directly addressing many of the complex scientific and regulatory challenges for effective chemical management policies.



## 1.0 Introduction

The ICCA-LRI in conjunction with the JRC held its 2010 workshop, *Integrating New Advances in Exposure Science and Toxicity Testing: Next Steps*, on 16 and 17 June 2010 in Stresa, Italy. A major driver for this workshop was recognition that true progress in decision making about the safety of chemicals will require not only advancements in exposure science and toxicity testing but also cross-disciplinary understanding between these two areas. Another driver was the need for critical improvements in communication between scientists and decision makers, and with stakeholders, including the public, so that better chemical management policies and practices can be developed. This workshop, which convened more than 120 participants from government, academia, non-governmental organizations, and industry representing 19 different countries, is the sixth in this annual series.

The program for the one and one-half day workshop, including the list of the speakers and titles of their presentations, is provided in Appendix B. Plenary session presentations during the first morning set the stage for additional presentations and discussions during the parallel breakout sessions on the three workshop themes in the afternoon. The themes for the breakout sessions were exposure science, toxicity testing, and communicating scientific information. A poster session during the evening of the first day showcased research from an internationally diverse group of presenters. A list of the posters presented is included in Appendix C. The three breakout sessions continued on the second morning and workshop participants then reconvened for the closing plenary presentations. The session began with summaries of the breakout session presentations and discussions from each of the session rapporteurs and concluded with the plenary speakers. After the close of the workshop, workshop participants were invited to attend an optional tour of the JRC's laboratories and facilities in Ispra, Italy.

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

## 2.0 Welcome Remarks

Workshop co-chair, Maurice Whelan from the JRC, welcomed the attendees and expressed his enthusiasm about the opportunity to co-organize this workshop with the ICCA-LRI. He said that he was looking forward to the presentations and to a productive workshop. Janet Mostowy, Chair of the ICCA-LRI Planning Group, then thanked the JRC for all of its efforts in the collaborative planning of the workshop. She provided an overview of the LRI, describing it as the chemical industry's investment in a sustainable future that combines ground-breaking research, scientific outreach, and initiatives that

protect public health and the environment. She commented that the LRI regional programs in Europe, the United States, and Japan were currently focused on three research areas: emerging technologies, exposure science, and translation relevant to health and environment. She encouraged attendees to visit the ICCA-LRI Web site for further information about the LRI program and the regional activities.



Workshop co-chair, Maurice Whelan, welcomes attendees.



## 2.2 Plenary Session I – Integrating Science for Chemical Safety Assessment

Annette Guiseppi-Elie, workshop co-chair and a member of the American Chemistry Council's LRI Strategic Science Team, began by extending a welcome to the international group of more than 120 attendees who represented 19 countries. She commented that this was the sixth workshop in the annual ICCA-LRI annual series. It was, however, the first co-organized with the JRC and reflected the mutual interests between the two organizations to improve the efficacy of chemical safety assessments. She summarized the objectives and anticipated outcomes for the workshop by stating that they were to discuss and integrate information about emerging developments in exposure science and toxicity testing to advance knowledge-based decision making about the safety of chemicals. The workshop objectives also included evaluating how communication between scientists and decision makers, and with stakeholders, including the public, can be improved to yield better chemical management policies. She then reviewed the workshop program and the format for the breakout sessions on exposure science, toxicity testing, and communicating scientific information.



Workshop co-chair, Annette Guiseppi-Elie, explains the collaboration between LRI and JRC.

Maurice Whelan then provided an overview of his organization, the JRC, noting that its primary role as the Directorate-General of the EC is to provide customer-driven scientific and technical advice to support EC decision making. As one of the seven institutes in five member states, the Institute of Health and Consumer Protection, located in Ispra, Italy where he is based, has a staff of approximately 300 that conduct research to support European Union (EU) legislation involving risk assessment as well as cross-cutting legislation and issues. He proceeded to outline a number of current challenges for the JRC, beginning with legal definitions for hazards and substances, such as endocrine disrupting compounds and nanomaterials (NM). Challenges for these two examples include establishment of criteria for their identification and assessment, particularly for NM where legally clear, unambiguous, and enforceable language is needed. Reducing animal testing is another major goal for the EU with its ultimate aim to replace animals with alternative methods. He commented that current EC regulations for cosmetic products and ingredients establish imposing timelines for bans on animal testing within the next few years that will be challenging to achieve. He also noted that mode of action (MOA) and pathway-based toxicology are current concepts in understanding the effects of chemicals, yet the processes for incorporating them into decision making for chemical management are not yet defined. Another challenge is how to exploit the new technologies in science from a regulatory perspective. Many questions remain regarding how to use the information from cell and tissue models, functional assays that assess biological function, automated assays, metabonomics, and computational toxicology in ways that are relevant to regulatory decision making. He commented that all of these challenges can be met if stakeholders practice good science and good sense, keep the purpose and customers in mind, and combine knowledge, methods and disciplines. He concluded that is important to remember that this is not a project, but a journey.

The next plenary speaker, Alan Boobis from Imperial College, posed the provocative question whether integrating science for improved chemical safety assessment is myth or reality. He listed a number of current drivers for this objective, including increased expectations from consumers for minimal health risks, limited resources due to the economic conditions, and advances in the 'omics' technologies and computational capabilities for data analyses. He noted that safety assessment under the EC's



Registration, Evaluation and Authorisation of Chemicals (REACH) legislation relies on science-based risk assessment to establish whether harm is likely to occur following actual or predicted exposures to chemicals. Its goal is not to eliminate chemicals but to assure consumers that they are safe to use. However, he cautioned that both false negative and false positive information from chemical testing for safety assessment could have serious implications for human health. He also commented on a new paradigm of activation of toxicity pathways that was described in the 2007 National Research Council (NRC) report, *Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy* (NRC 2007) and noted the potential complexities involved in toxicity pathway analysis. He listed MOA and key events for chemicals, host susceptibility factors, selection of developmental stage for testing, and understanding the differences between adaptive and adverse reactions in the test results as complicating factors in chemical safety assessment. In closing, he stated the vision of the 2007 NRC report is potentially achievable in the long-term if sufficient resources and intellectual input are applied and a substantial investment in mechanistic research is made. He cautioned that the timescale for contribution of scientific advances to risk assessment is usually underestimated. In the near term, the pressing need is for shorter term strategies that focus on integrating biology into MOA at the level of key events.



Alan Boobis discusses integrating science into chemical safety assessment.

Caron Chess from Rutgers University then reviewed the role of communication in decision making. She noted that a 1996 NRC report, *Understanding Risk: Informing Decisions in a Democratic Society* (NRC 1996) described risk characterization as an iterative, analytical, and deliberative process that is decision-driven and that can enhance organizational capability. Successful characterization of risk for chemicals will require getting the science and the participation right as well as getting the right science and the right participation. The process has to satisfy the participants and be responsive to their needs. Organizations must also evaluate how much risk communication is needed, how much to evaluate themselves; they must also understand the level of commitment and expertise needed for an analytical and deliberative process. She commented that the 2008 NRC report, *Science and Decisions:*



Caron Chess speaks about the role of communication in decision making.

*Advancing Risk Assessment* (NRC 2008), recognized several key organizational issues. They included a high level of commitment by the agencies and staff, a clarity of purpose, appropriate expertise, and a continuity of personnel so that the process will be effective. More research is needed to develop a common framework for these types of participatory processes and the 2008 NRC Report is a good start. To implement this report's recommendations, governmental agencies and industry must begin to develop and evaluate the processes. Although this effort requires motivation, the recent will and efforts directed towards the 'omics' are a good example that this can be achieved.



## 2.2 Plenary Session II – Setting the Stage for the Breakout Sessions

The presentations in this session provided background and overviews for the three workshop themes of exposure science, toxicity testing, and communicating scientific information that would be discussed in greater detail during parallel breakout sessions.



Matti Jantunen discusses exposure science for health management.

The first speaker in this session, Matti Jantunen from the National Public Health Institute's Department of Environmental Health, reviewed different perspectives about everyday exposures to chemicals and then questioned whether or not these exposures increase our health risks. Intriguingly, his answers were both yes and no. He commented that humans are increasingly exposed to unknown chemical cocktail mixtures in consumer goods that are manufactured in countries with poor chemical regulatory controls. Humans are also exposed to chemical mixtures from products treated with chemicals intentionally designed to improve the look, feel, or fire resistant properties of materials. Finally, the myriad of medicines taken for health concerns,

which are specifically designed as biologically active chemicals, is another source of exposure in everyday life. He also noted that many chemicals, such as vitamins and medicines, can produce beneficial effects at the proper dosages. He went on to outline the concept of the exposome, first defined by Wild (2005) as the total exposures for an individual over a lifetime, and commented that both the exposome and the genome contribute to our responses to chemical exposures. He further commented that measuring exposures to complex mixtures, such as particulate air pollutants and diesel exhaust, is an invasive, work intensive, and expensive process, but not technically or scientifically difficult. The greatest challenge for assessing complex exposures is that their sources can be different, variable, and independent. When both chemical hazards and exposure conditions are understood, exposure-based risk management processes can be used to minimize health risks. He continued that risk assessment and risk management of complex exposure mixtures requires pragmatic rather than theoretical approaches. Effective implementation of such approaches can yield acceptance of certain levels of risk in return for the potential benefits.

The next plenary speaker, Stefan Przyborski from Relnervate, discussed new technologies designed to enhance cell-based *in vitro* testing methodologies and improve predictive toxicity. He described the development by his company of a three-dimensional porous and stable polystyrene scaffold for *in vitro* assays and suggested that this product advances how such assays can more closely resemble *in vivo* form and function. He then reviewed results from growth, viability, and functional assays for different types of cells and cell mixtures grown on the scaffold and described the adaptability of the polystyrene matrix for various cell growth and analysis applications. He stated that the three-dimensional nature of the scaffold better mimics the natural environment of cells in the body and allows cells to grow in a more natural manner compared to traditional two-dimensional cell culture plates and wells. He proposed that such improvements in cell culture technologies can improve



Stefan Przyborski speaks about new technologies to improve *in vitro* testing and predictive toxicology.



the accuracy of *in vitro* assays and advance research as well as reduce research and development costs for academic and industrial sectors.

Biological susceptibility and cellular elasticity was the topic for the next plenary speaker, David Epel from Stanford University. He opened his presentation by reviewing some of his previous studies on marine organism embryos. These studies determined that the embryos are normally well protected against historical, anticipated, and predictable environmental stressors and exposures; problems arise when the environment changes. He went on to outline several examples of exposures of human embryos to medical treatments, including thalidomide and diethylstilbestrol, that resulted in adverse developmental outcomes after birth. His introduction then led to a discussion of management of toxic chemicals by the body through several mechanisms. First,



David Epel discusses biological susceptibility and cellular elasticity.

toxics can be transformed by cellular systems, such as cytochromes, into less toxic compounds. He also described barricade approaches with broad substrate specificity that are present in the cellular membranes of several organs, such as the brain, gut, kidney, and placenta; these barricade approaches can prohibit cellular entry of toxicants into the cells without altering the toxicants. Another mechanism is a bouncer approach in which efflux transporters bind a toxicant that has entered the cell to another molecule and then transport it outside of the cell. As in the case of marine embryos, changing conditions can subvert these normally protective mechanisms and examples include exposures to pollutants, novel chemicals, high toxicant levels, and toxicant mixtures. The speaker emphasized that an improved understanding of these protective mechanisms can provide a new view on bioaccumulation in which efflux transporters can alternatively become “garbage collectors” when the cell is unable to pump out a toxicant. In summary, increasing the knowledge about embryo and cellular defenses contributes to an overall understanding of the implications and outcomes from toxicant exposures.

Redefining adverse effects and linking *in vitro* toxicity testing results to risk assessment was the topic for the next speaker, Mel Andersen from The Hamner Institutes for Health Sciences. The context for his presentation was the 2007 NRC report, *Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy* (NRC 2007), and its focus on improving toxicity testing for environmental agents to which humans are exposed. The major goal of the NRC committee members who prepared this report was to review the drawbacks of current toxicity testing systems, such as the standard two-year rodent bioassay, and to provide innovative approaches that could move beyond its drawbacks. Their findings recommended a shift towards use of toxicogenomic and bioinformatic approaches to decrease costs and animal use and to increase the numbers of chemicals that could be evaluated. These new approaches would be essential for identifying toxicity pathways and the early cellular events that may be key in subsequent development of disease. The members also recognized that this shift away from animal



Mel Andersen presents perspectives on linking *in vitro* test results to risk management.

testing would be a true journey requiring conviction and that the challenges presented would provide



opportunities to do the job right. He also described a failure analysis approach that could be relevant to understanding the series of events that lead from chemical exposure to adverse events in cells and organisms. In his “Swiss cheese” model of failure analysis, he proposed that failures within the different layers of safety defenses in cells and organisms could be represented by holes in a series of cheese slices. When the holes line up through these layers of defenses, it represents the potential for an exposure to produce an adverse outcome. He concluded that one goal for use of the new technologies is to identify those pathways in cells that are important in the development of key adverse toxic events. The database now being created must be mined systematically to determine the latent and active failures that can result from a toxic exposure. Such information will be essential for determining safe levels for chemical exposures that do not exceed the capacity of the defense systems.

The final speaker for this plenary session was Bette Meek from Health Canada and the University of Ottawa and she discussed integrated tools for the next generation of risk assessment. She commented that since the four-step paradigm for risk assessment was originally proposed in 1983 by the NRC (NRC 1983), the majority of time and effort in risk assessment has focused on the first step, hazard identification. She stated that efforts now should shift not only towards exposure assessment, the second step in risk assessment, but also towards effective and efficient risk management. She then reviewed the processes, tools, and triage system used



Bette Meek reviews integrated tools for risk management.

to categorize approximately 23,000 chemicals on Canada’s Domestic Substances List, a project that required completion by 2006 to comply with the 1999 Canadian Environmental Protection Act. In brief, they categorized and ranked all 23,000 substances using a score developed for each substance based on its use and its relative ranking for potential exposure (highest, intermediate, and lowest). Lessons learned from this process were that simple chemical use profiling can be a discriminating tool; differences between consumer and environmental exposures are important; chemical use correlates better with exposure potential than the production volume of a chemical; and early and iterative use profiling is important. She commented that predictive tools and models, such as physiologically-based pharmacokinetic (PBPK) models, will be important elements for advancing risk assessment. A barrier to their use has been a lack of communication between model developers and risk assessors to clearly explain to the risk assessors how the models work. Elements to move the process forward include additional expertise and training for risk assessors as well as an application of general principles of performance and evaluation for the models and transparency in the processes. She closed by saying she was optimistic about the availability of more predictive tools that draw on improved biological knowledge to meet the needs of regulatory risk assessment; “collective” leadership will be needed in the short and long term.



### 3.0 Breakout Sessions

The breakout sessions were designed to provide forums for interactions and discussions among the participants on each of the three workshop themes. Participants were free to attend any of the three breakout sessions, which ran in parallel. Participants were also provided with breakout session guides prior to the workshop that contained questions as starting points for the discussions. In brief, the themes for the three sessions were:

- **Exposure Science.** Consider relevant research activities for addressing gaps in exposure science required to meet both immediate needs for rapid prioritization as well as longer term objectives for chemical evaluation and risk management.
- **Innovative Approaches to Generating, Integrating, and Interpreting Hazard Data.** Examine new experimental cell systems and computational analytical and integrative methods for predictive toxicology and utilization to support chemical assessment
- **Communicating Scientific Information.** Develop a framework for a research agenda to determine how the scientific information exchange between decision makers, scientists, and the public can better meet the needs of society.

#### 3.1 Breakout Session 1 - Exposure Science

##### Day 1: Chemical Evaluation for Public Health Decisions

The chair of this breakout session, Elaine Cohen Hubal from the U.S. Environmental Protection Agency (EPA), opened the session by providing an overview of EPA's National Center for Computational Toxicology (NCCT). The goal of this center is to integrate computational and informational technologies with molecular biology to improve prioritization and risk assessment for chemicals. An important focus of this goal is to incorporate hazard and exposure information in risk assessments to make more informed public health decisions. ExpoCast™, a key program within NCCT, focuses on using exposure science for chemical prioritization and toxicity testing. It was designed as a complement to EPA's ToxCast™, a program that includes high throughput screening assays and has been an important resource for new *in vitro* data to improve understanding of chemical toxicity. A main point of the presentation was that hazard data must be integrated with exposure information to effectively prioritize chemicals and to identify those chemicals that will require additional testing and monitoring. Two objectives for ExpoCast are accessible and linkable databases as well as exposure-based screening tools that can accelerate chemical prioritization. ToxCast has already developed its Aggregated Computational Toxicology Resource (ACToR) database that contains both historical and current hazard information. NCCT is currently designing a prototype of a database containing exposure information called ExpoCastDB that will be added to ACToR. With regard to exposure-based



Exposure Science breakout group participants.



screening tools, NCCT is developing an integrated chemical prioritization scheme called ToxPi. This tool is based on a numerical index and provides a visual representation of multiple domains of information about a specific chemical. It can be used for chemical ranking and is adaptable to different prioritization tasks. Advances in exposure science like these will be needed to realize the goals described in *Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy* (NRC 2007). Other important issues that exposure science must address include understanding the effects of low dose exposures and the impacts of chemical exposures during windows of susceptibility on long-term health. Determining how mixtures of chemicals and multiple stressors alter susceptibility and response are other areas for more research.



The next presentation by Sumit Gangwal from the EPA provided more information about the ToxPi platform that was developed as a flexible and transparent framework to visualize data emerging from ToxCast. He stated that the results of a ToxPi evaluation for a given chemical are represented as a unit circle containing numerous slices, each of which represent a piece or related pieces of information. Examples of data categories that comprise the circle segment include chemical properties, *in vitro* assay results, pathways, and disease classes. For each slice, the distance extending from the circle's center is proportional to a normalized value of the component data comprising that slice, such as assay potency or predicted bioavailability; the width of the slice indicates the relative weight of that slice to the overall ToxPi calculation. The speaker then presented

an overview of ToxPi results incorporating exposure information sorted by endocrine activity score for approximately 200 of the ToxCast Phase I chemicals, most of which were pesticides. He concluded by stating that ToxPi profiles can provide visual representations of the relative contribution of all information sources to an overall priority ranking and that the approach is readily adaptable to diverse chemical prioritization tasks. Future directions for ToxPi development include incorporating more exposure information, such as manufacturing volumes, non-agricultural usage, measurements in food, and biomonitoring data, into the calculations.

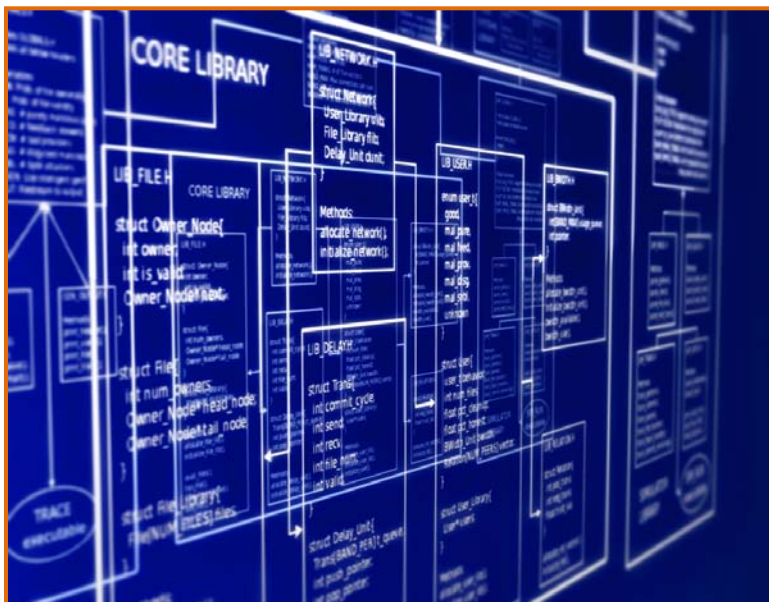
The German human biomonitoring effort and the EU project Consortium to Perform Human Biomonitoring on the European Scale (COPHES) were the topics for the next speaker, Marike Kolossa-Gehring from the Federal Environmental Agency (UBA) in Germany. She noted that chemical legislation in Germany places great emphasis on human biomonitoring as an essential tool for risk assessment concerning the safety of chemicals and the protection of public health. She went on to provide an overview of the German Environmental Specimen Bank and the German Environmental Surveys (GerEs), which are cross-sectional population studies. These studies have been conducted regularly since 1985 to generate exposure data to chemicals, to observe time trends, to identify potential health impacts, and to evaluate policy measures, such as those concerning REACH. To further increase knowledge about the internal exposure to chemicals among the German population, the Chemical Industry Association (VCI) together with the UBA and the Environmental Ministry began a unique initiative in 2010. Through this initiative, industry will develop new analytical methods for substances with potential health relevance or substances to which the general public might be exposed but are not yet measured. These methods will then be applied in population studies by the UBA. She



commented that a current challenge is harmonizing biomonitoring efforts across Europe so that resources can be used efficiently. Therefore, the objective of the EU COPHES project is to test the hypothesis that human biomonitoring can be performed using a coherent and harmonized approach across Europe. Her overview also included a review of the European partners for the project, the study design, and the biomarkers selection process.

The next presentation by Natalie von Goetz from ETH Zürich discussed modeling consumer exposure to environmental chemicals. Her presentation focused on aggregate exposure modeling, an approach that considers the exposures to one chemical from all sources through inhalation, dermal, and ingestion pathways. The research goals for the aggregate exposure modeling she described include determining maximal consumer exposures so that risk thresholds can be calculated and identifying the consumer groups at greatest risk. By including the contribution from different sources and pathways and by complementing this assessment with human biomonitoring data, appropriate risk mitigation strategies can be designed. Another goal is prospective modeling for new substances to identify upcoming future risks. These studies often consider a wide range of consumer products and foods as potential sources. As examples of the aggregate exposure modeling approach, she described results from a case study with bisphenol A that predominantly considered exposures from food sources; another case study primarily considered exposures from engineered nanoparticles in cosmetic and personal care products. She concluded that current issues for chemical exposure modeling include accounting for the uncertainty in risk assessment and effectively reducing model and parameter uncertainty. Linking external exposures and internal effects also remains as a current challenge.

A chemical screening visualization tool and its application to product evaluation and commercialization was the next topic discussed by Mario Chen from DuPont. He stated that the objective of his approach, called the Chemical Screening Visualization Tool (CVST), is to give a screening level view of the potential concerns of stakeholders regarding chemicals. CVST is a web-based chemical search system that is linked to the METanomics Information System (METIS) that contains more than 700 databases and regulatory lists. CVST incorporates this information and collates it into a comprehensive view that represents relevant environmental, hazard, and societal endpoints for industrial chemicals; the scoring system utilizes regulatory criteria, thresholds, and classifications. Similar to the ToxPi approach previously described, the visual output for each chemical is a unit circle containing different slices, each of which represent one piece or related pieces of information. The speaker's key point was that the CVST is a screening tool that highlights specific chemical parameters and endpoints; it is not a tool for final decisions. He commented that a current focus for CVST is chemical screening for product registration and that chemical screening can be applied throughout the product life cycle. CVST can be a useful tool to identify potential data gaps for chemicals and to develop integrated testing strategies.





The last presentation on this first day of the breakout session was by Juan Garcia Serna from University of Valladolid who discussed new trends in green engineering. He opened his presentation by commenting that the goal for green engineering is sustainability; green engineering should meet present needs without compromising either the potential for future generations to meet their own needs or the health of the planet. He explained that a current perspective on sustainability is that impacts on the economy, the environment, and society are all integrated and they all must be considered. A survival kit for green engineering that he proposed contained several elements, including a unified definition of sustainability. He also discussed sets of principles and tenets, including those for energy use and efficiency, inspiring philosophies, such as inherently safer design and biomimicry, and use of effective management and technical tools. He closed by stating that the most important factors for achieving the goals of green engineering are creativity, education, and commitment.

### *Day 2: Integrating Exposure and Health Sciences for Better Decisions*



The second day of the exposure breakout session began with a presentation by Martyn Smith from the University of California Berkeley on use of 'omics' to characterize human exposure. He commented that cancer and degenerative diseases result from a combination of genetic and environmental (G x E) factors. While 10 to 30 percent of disease incidence is likely contributed by genetic factors, 70 to 90 percent is likely contributed by the internal chemical environment, which is influenced not only by exposures to chemicals but also by radiation, diet, drugs and stress. He stated that the exposome (Wild 2005) is a new concept defined as the total of an individual's exposures over an entire lifetime. Traditional exposure assessment could be considered 'bottom-up exposomics' where one measures all exposures, determines the exposure conditions an individual has experienced, and then uses sophisticated modeling to determine the exposure. In 'top-down exposomics,' a blood

sample or other sample from the body could be analyzed to identify signatures of exposure. The signatures selected would depend on the target of the exposures, such as an adductome to measure all deoxyribonucleic acid (DNA) adducts or telomere length to measure stress. In this way, adductomics, transcriptomics, and other 'omics' technologies could be applied to characterize the exposome for specific diseases. This concept dramatically shifts the paradigm away from a chemical-by-chemical approach to identify the causes of diseases and aims to include endogenous as well as exogenous exposures. To advance this concept, new technologies that can analyze nucleic acids and proteins in a drop of blood are needed, as well as an international government-industry-academic alliance that would be a human genome project for the environment. He concluded his presentation by proposing that this Human Exposome Project would develop new tools to assess all exposures at all life stages, quantify susceptibilities, identify G x E interactions, and use bioinformatics to analyze the resulting data.



Dean Jones from Emory University next spoke on the topic of high-throughput metabolomics. He opened his presentation by stating that the Predictive Health Institute at Emory focuses on health as a state of well-being and vitality, not simply an absence of disease. Predicting the future health of an individual requires retrospective information about exposures and factors that can impact health status. He reiterated the perspective by the previous speaker regarding the need for an international Human Exposome Project as well as the need for a conceptual framework for systematic analyses and high-throughput technologies to evaluate human exposures. He commented that the profiles of individuals' metabolites integrate the effects



of diet, lifestyle, and environment on the genome as well as provide mechanistic information useful as biomarkers of exposure and health outcomes. He went on to describe some examples of automated top-down metabolomics approaches that can use human samples, such as blood, to provide extensive profiles that contain thousands of chemical metabolites reflecting previous chemical exposures. He concluded by commenting that top-down metabolomics provide an approach to study the exposome. It will be valuable in the context of systems biology of the individual and an important foundation for personalized medicine and predictive health strategies.

Toby Athersuch from Imperial College London next discussed advancing metabonomic techniques for assessing environmental effects on human health. He first described the Centre for Environment and Health, a joint center between his college and Kings College London, that integrates elements of toxicology and exposure assessment to evaluate links among exposures, disease, and population health and to inform environmental health policies. He distinguished between metabonomics, which is the quantitative measurement of the complex response of living systems to pathophysiological stimuli or genetic modification, and metabolomics, which is the complete, yet variable, set of metabolites in a cell, tissue, organ, or organism. Metabonomics operates at the metabolic interface between a system's biology and its environment and changes can reflect early consequences of exposure. As an example of this approach, he described a metabolic profiling study in an uncontrolled human population that successfully identified intermediate biomarkers of response to cadmium at realistic concentrations relevant to actual environmental exposure levels. This study demonstrated for the first time the use of pathway analysis mechanisms to combine 'omics' technologies and metabolic data and identify linkages between exposure and disease end points. He summarized by stating that metabolic profiles are information-rich phenotypes; they can help define the interactions among genes, environment, and lifestyle that determine disease risk and onset. Improved instrumentation and novel statistical and pathway integration methods can also provide better opportunities for biomarker discovery to advance this approach.

The next presentation by Soterios Kyrtopoulos from the National Hellenic Research Foundation discussed the potential of 'omics' technologies for population studies. In his opening comments, he noted that the advantages of current biomarkers for population studies are that they are sensitive and chemical-specific indicators of exposure; the disadvantages are that a variety of assays and



technologies are needed for the various endpoints and that information about disease mechanisms is limited. However, the 'omics' may present a new generation of biomarkers with numerous potential advantages. They can utilize generic technology that is independent of disease or exposure and they can evaluate large datasets for global, untargeted searches to identify biomarkers without prior hypotheses. In addition, they can provide mechanistic information on multiple endpoints and, in combination with bioinformatics, can provide a systems biology approach to biomarker discovery. The disadvantage is that there is limited experience using this 'omics' approach. With this as background, he went on to provide an overview of the EnviroGenomarkers Project, a four-year project in its first year that will use three cohort groups in Europe. This study will combine 'omics' technologies with bioinformatic approaches to identify new biomarkers of exposure to toxic environmental agents and new biomarkers of disease. One focus of this study will be to identify potential associations between exposures to polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons, and cadmium and development of breast cancer and between exposures to PCBs and B-cell lymphoma. The pilot study for this project is nearing completion; the ongoing challenge will be to determine the feasibility of using 'omics' technologies to successfully identify biomarkers of disease in large-scale population studies.

### *Breakout Session Discussion*

The leader for this discussion, Peter Boogaard from Shell, requested that the breakout session participants consider two aspects of relevant research activities needed to address the gaps in exposure science. The first was the activities needed to meet the immediate needs for rapid prioritization and the second was the research needed for longer term objectives in chemical evaluation and risk management. The questions listed in Figure 2 served as starting points for the discussion.

The participants thought that, at a minimum, an opportunity existed for a sharing of resources that could include both knowledge and technology. As an example, they thought that rather than shipping samples, transcriptomics could be conducted anywhere; they also noted that the human genome project is a resource for a large number of technologies that could be used. It will be necessary to think about what populations might be appropriate targets for studies. Although conducting a population study may not be feasible, a proof of concept study could be considered. Studies in developing countries should also be considered because the exposures would be very different; this approach could also take advantage of international aspects and could collect samples from melting pots of individuals with very different backgrounds.

### **Figure 2. Question for the Exposure Science Breakout Session**

- How does the exposome approach and associated technologies inform public health decision making?
- What is the difference between biomonitoring and the exposome?
- Can the exposome be used to provide information required to make decisions at the general population level? At the individual level?
- Will the exposome provide information required to address the full range of environmental health questions?



A concern expressed by some participants was that the investigative and research resources have been misplaced and that the regulatory focus on environmental health issues that is not that important; as a result, opportunities are lost. One suggestion was to combine existing information to create an international biomonitoring program and to identify the most relevant and beneficial issues and be a better focus for our resources. Currently, several key target exposures, such as particulate matter, environmental tobacco smoke, ozone, and lead, could be addressed and the results could have a tremendous impact on public health.

The exposome was noted as an organizing principle for exposure science. This emerging concept will involve a major shift in thinking from the traditional exposure science approach of chemical to individual to a new approach that starts at the biology and goes back to sources. A major current challenge is how to move forward in the transition from source to receptor towards disease to source. This is one goal for the National Academy of Science Exposure Committee because a move forward from traditional exposure assessment is essential. It will be also be important to be conscious of how to interpret the new information.

### *3.2 Breakout Session 2 – Toxicity Testing*

#### *Day 1: Emerging Models for Human-based Toxicity Testing*

Timothy Gant from the Medical Research Council and the University of Leicester, who served as the chair for this session, began by commenting that a disconnect exists in the general public between the need and desire for new chemicals that can support an increasing population and an improved quality of life and the concerns about the potential health risks from product use. He also commented that the public appears to have a much greater sense of risk than benefit from chemical use. He stated that new technologies are enabling the collection of much more data on the effects of chemicals in biological systems; however, the interpretation of this data is lagging and maybe contributing to an increased sense of risk. Finally, he noted that the transfer of these new methods into the testing process is being hampered by the time taken for validation and that this situation might be improved through ‘validation by use.’ He asked the attendees to consider the questions provided to them prior to the workshop and listed in Figure 3 as they participate in the breakout session.

The first presentation in this session was by Julia Gorelik from Imperial College who discussed a new scanning microscope technique for functional characterization, manipulation, and monitoring of living stem cells. Her approach used scanning ion conductance microscopy (SICM) as an imaging device to study the changes in surface, volume, and height in living embryonic stem-cell derived heart cells, termed cardiomyocytes, at high resolution. She evaluated the addition of media containing elevated levels of bile acids to mouse and human cardiomyocytes to mimic conditions associated with obstetric cholestasis during the third trimester, a condition that can cause fetal cardiac pathology. She





demonstrated that less mature murine and human cardiomyocytes were more susceptible to bile acid-induced arrhythmias. She commented that this technique could be useful for defining disease mechanisms, testing potential therapeutic agents, and defining the genetic and epigenetic contributions to the susceptibility of some pregnancies to cholestatic intrauterine fetal death. She also combined the SICM method with smart patch clamp techniques to evaluate the cardiomyocytes and determined that she could identify nerve synapses, pre- and post-synaptic membranes as well as record ion channels. She concluded by commenting that the methods described offer innovative approaches to study living cells under different conditions and to evaluate a variety of disease processes.

### Figure 3. Questions for the Toxicity Testing Breakout Session

- Will differentiated embryonic stem cells provide a better *in vitro* system in which to understand chemical toxicity than the systems currently available?
- Does any of the imaging methods presented have utility in chemical risk assessment?
- What is the potential application of NMR based methods in understanding and assessing chemical toxicity?
- What is the potential and what are the challenges for these toxicity tools to enable predictive toxicology and a better dose-response characterization?
- How do these models address low dose and no threshold effects in toxicity testing?
- Significant amounts of data already exist and, and additional data are emerging. Are the wheels of data interpretation and integration struggling to cope with the output from the engine?
- Is there enough training in new methodologies and data interpretation to serve the needs of the industry now or in the future?
- What role does, and will, computational cheminformatics play in chemical risk assessment?
- How important is understanding mechanisms?
- How do you extrapolate from cell systems to whole organisms? Is this necessary for making good risk assessments decisions, or can a new paradigm be constructed such that points of departure and risk decisions can be made based on signals from the cell-based assays?
- How do we integrate toxicity testing data with emerging exposure tools for better decision making?



The next speaker, Claudia McGinnis from Roche, discussed applications of human embryonic stem cell (hESC)-derived liver cells, or hepatocytes, for toxicity testing. Specific areas of interest for the pharmaceutical industry include their use in absorption, distribution, metabolism and excretion studies and in drug development and drug safety studies. A goal for the use of the hESC-derived hepatocytes is to mimic *in vivo* hepatogenesis, including specification, proliferation, commitment, differentiation, and functional maturation. She also discussed a variety of advanced cell culture and co-culture techniques that could be used to improve cell differentiation and survival *in vitro*. She noted that the method selection would depend on the specific situation, as well as other considerations, such as complexity, survival time, and organotypic characteristics.



Christiane Guillouzo from the Université de Rennes continued the session's discussions on stem cell-derived hepatocytes and their uses in toxicology. She focused on HepaRG, a new cell line developed at her university with attributes that include origin from a human solid liver tumor and an intermediate phenotype that suggests an immature progenitor cell origin. She noted similarities between HepaRG cells and primary human hepatocytes and that a high level of cellular differentiation could be achieved by adding dimethyl sulfoxide, a compound that induces maximum morphological differentiation, polarity, and drug metabolism functions. Cellular functions that can be observed in the HepaRG cells include plasma proteins production, glycogen metabolism, lipid metabolism, and detoxification. She proposed that HepaRG cells are a good alternative to human hepatocytes and that they have multiple applications for developmental cell biology and virology as well as short-term and chronic toxicology studies, including those that evaluate mutagenesis and carcinogenesis. She concluded that the HepaRG cell line could be a useful tool to define conditions for deriving hepatoblasts from hESCs. The line could also serve as an experimental tool to better understand the mechanisms that control maintenance of embryonic stem cell renewal and aging and the immortalization process by which the cells override normal growth control mechanisms. HepaRG cells can be an effective model for understanding hepatic detoxication metabolism and for comparing differences in cells during developmental stages and mature stages.

The effects of chemicals on tissue-specific homing by T cells was the topic for the next speaker, Makoto Iwata from Tokushima Bunri University. The focus for the research project he discussed was better understanding the role of Vitamin A and T cells in preventing the persistent diarrhea that can occur during conditions of chronic under nutrition. He noted that in normal diets, Vitamin A helps to maintain the integrity of mucosal epithelia, enhances immunoglobulin A responses required for gut immunity, and plays a critical role in deploying lymphocytes into the gut tissues. To address his research question, he used vitamin A-deficient mice produced by feeding them vitamin A-deficient diet. Through his animal model, he determined that T-cells acquire their gut-homing specificity when they are activated in the gut-related lymphoid organs and that differential expression of the homing receptors



on T cells is affected by the presence or absence of retinoic acid, a metabolite of vitamin A. As a result, Vitamin A deficiency can reduce number of T cells that are positive for immunoglobulin A in the small intestine. He also observed that environmental chemicals may disturb retinoic acid production and that the effects of chemicals on retinoic acid may cause immune disorders by affecting lymphocyte homing and the functional differentiation of T cells. These studies contribute to the understanding the role of Vitamin A and T cells to maintain normal intestinal conditions and the potential effects of environmental chemicals.

The final speaker for the afternoon session was Mia Emgard from Cellartis who discussed cellular models for cytotoxicity and developmental toxicity that use human pluripotent stem cells (hPSC). She reviewed three screening models developed by Cellartis that are based on hPSC and designed to evaluate developmental toxicity, cardiomyocyte toxicity, and hepatocyte toxicity. The developmental toxicity model is a medium/high-throughput assay using hPSC that has evaluated 25 compounds to date. It looks at the half maximal inhibitory concentration ( $IC_{50}$ ) and the goal is to predict correlations between cell viability and morphological signs of toxicity. The cells in the hPSC-derived cardiomyocyte-like cell model express cardiac markers and ion channels. These cells also display action potentials and respond to pharmacologic stimuli, characteristics that are useful for studies on cardio-active drugs and substances. The hPSC-derived hepatocyte-like cells have demonstrated the ability to modulate into different phases, such as endoderm, hepatic progenitor, or mature hepatocyte, based on culture conditions and exogenous factors. They also display cytochrome enzyme activity following incubation with specific cytochrome P450 substrates. The overall goal for this work and these models is to develop cell-based products that can be used as *in vitro* tools for drug discovery.

### Day 2: Computational and Integrative Methods for Predictive Toxicology

The opening speaker for the breakout session on the next morning was Christopher Wierling from the Max Plank Institute for Molecular Genetics who discussed a Monte Carlo strategy for systems biology of cancer treatment. He stated that the goal of this work is to develop mathematical models of cellular processes, transcription and translation, and downstream processes using biochemical reaction network information and reaction kinetics. The models set up ordinary differential equations to represent biochemical reactions, such as glycolysis and gene regulatory processes, and use publicly-



Systems toxicology laboratory at JRC.

available pathway database resources from the internet and a software package called PyBioS developed the Max Planck Institute to run these equations. The system generates models for *in silico* simulation and the user can visualize the interaction network and also select specific reactions within the system. The researchers identified several pathway databases and tried to integrate these databases into a common database that reflects results of the different individual databases, called ConsensusPathDB. To develop mathematical models related to cancer, the researchers began by looking at the signal transduction pathways and uploading the information into a simulation system. To



resolve a problem that emerged due to a lack of information about all of the individual kinetic parameters, the researchers developed a Monte Carlo approach for a normal state and a treatment state. Researchers then used next-generation sequencing to identify the mutation pattern in different cancer patients and produce an *in silico* tumor situation. The effect of individual inhibitors and drug combinations could be combined with a certain cancer state to show an individual's profile and the potential outcome of the treatment. This Monte Carlo strategy presents a promising approach for evaluating drug therapies for cancer patients.

The next speaker, Muireann Coen from Imperial College, discussed metabonomics for understanding mechanisms of toxicity and inter-individual response. She described metabolic profiling as a non-targeted approach that can demonstrate the effects that different toxins can have on different target organs using biochemical fingerprints that are organ specific and mechanism specific. An advantage is that these models can monitor metabolic indicators over time to follow onset, progression, and recovery from toxicity. Liquid chromatography/mass



spectrometry and nuclear magnetic resonance (NMR) are key tools for simplifying the data. A current project of the Consortium for Metabonomic Toxicology (COMET), which includes members from Imperial College and numerous pharmaceutical companies, has two phases. The first phase is a screening approach to generate metabolomic data and the second phase concentrates on the mechanism of toxicity using NMR, mass spectrometry, and transcriptomics. They are currently evaluating 147 toxins and treatments in rat and mice models using single and multi-dose studies for seven days. Their results indicate that metabonomics is useful approach for investigating toxic insult, including drug metabolism and endogenous consequences. She concluded her presentation by commenting that more validation studies are needed as well as integration with proteomic, transcriptomic, and genomic platforms.

Andrew Worth from the JRC next spoke about the use of computational methods in regulatory decision making. He opened his presentation by noting that the JRC is evaluating the use of qualitative or (Q)SAR methods and (Q)SAR-light methods in regulatory risk assessment. He then commented that computational methods can serve a role in risk assessment for several policy areas, such as REACH, cosmetics, and surface water protection. Computational methods can be useful for establishing chemical inventories, priority setting to focus resources for risk analysis, and for filling gaps in hazard and exposure data for risk assessments. He noted that the JRC has already developed several computational approaches and that they are free and publicly available on the JRC website. He briefly described several of these, including the database inventory of (Q)SAR models, toxicity estimation tool (Toxtree), a chemical similarity tool called Toxmatch, the chemical reactivity and fate tool (CRAFT), and decision analysis by ranking techniques (DART). Other available approaches that were developed by the Organisation for Economic Co-operation and Development (OECD) include eChemPortal and the (Q)SAR Application Toolbox. He stated that a critical need for developing reliable and reproducible high



Workshop participants visit the JRC *in vitro* methods laboratory.

quality models that are of interest to the JRC and to consumers is data. He concluded by commenting that the next important step will be to identify meaningful approaches to integrate information from (Q)SARs, 'omics', HTS and *in vitro* results to predict *in vivo* outcomes.

The topic for the next speaker, David Rouquie from Bayer CropScience, was a case study of endocrine disruptors and threshold effects. He noted that the context for the research he would discuss was the EU Plant Protection Products Legislation published in 2009 and its marketplace restrictions for substances with endocrine

disrupting properties. This case study was a data contribution by Bayer CropScience that used Flutamide, an anti-androgen compound used in the treatment of prostate cancer, as a reference compound. Flutamide blocks the androgen receptor in the pituitary gland causing increased production of leutinizing hormone and stimulation of the testis. He commented that this MOA is similar to fungicides like vinclozolin and procymidone. For their study, they gave rats a range of doses by oral gavage for 28 days and then conducted a variety of assays to determine the effects, including toxicity pathway analyses. He reported that Flutamide induced testicular toxicity and that they were able to identify thresholds for the observed effects. He concluded that the biological pathway analyses are helping them to better understand the continuum from normal to adaptive to adverse responses.

The final speaker in this session was Grace Patlewicz from DuPont who discussed computational toxicology from a (Q)SAR perspective. Her presentation included a case study on how (Q)SARs can be practically applied under REACH; a second case study reviewed how (Q)SAR information can play a role in integrated testing strategies (ITS). She defined ITS as endpoint-specific workflows that depict various steps in the collation and interpretation of toxicity information for a chemical to evaluate its robustness for different purposes, such as hazard identification for risk assessment. She stated that DuPont's approach had been first to gather available information for substances of interest to determine what data gaps existed and then to investigate the feasibility of using (Q)SARs to fill these gaps. They found that the most common data gaps were for environmental fate, physico-chemical properties, complex mammalian toxicity and ecotoxicity. (Q)SAR was found to be most useful for physico-chemical properties, environmental fate properties, such as biodegradation and ecotoxicity endpoints, such as acute aquatic toxicity. The first case study focused on the evaluation of an existing (Q)SAR for the logarithm of the octanol/water partition coefficient (Log Kow).

The goal was to demonstrate how this (Q)SAR model's validity could be characterized in accordance with the OECD principles and evaluated for a substance of interest to meet the conditions of use under REACH. A key message was that there exists considerable flexibility on the use of (Q)SARs so long as certain conditions are met. Depending on the model, the substance of interest and the specific question being addressed, (Q)SAR information may be sufficient to address an endpoint completely or contribute to part of a weight of evidence argument. The ITS case study focused on skin sensitization and explored the correlation between sensitization and mutagenicity from a reaction chemistry perspective. She concluded that commonality between the rate determining steps of mutagenicity and skin sensitization can be helpful to refine existing integrated testing strategies; such an approach can maximize the amount of information extracted from a minimum amount of experimental testing.



### 3.3 Breakout Session 3 – Communicating Scientific Information

#### Day 1: Addressing the Nodes of Disconnect

The chair of this breakout session, Lynn Frewer from Wageningen University, opened the session by reviewing its overall focus and goals and by providing an introduction to the concept of social impact assessment. She proposed a gap analysis to address the questions of where we are now and where we want to be regarding effective communication of scientific information among decision makers, scientists the public that can better meet the needs of society. She also asked the participants to review and consider the questions listed in Figure 4 as they listened to the speakers.

She began her presentation by noting that risk assessment as applied to health issues and to environmental issues should be transparent and explicit. What is implicit and not transparent are the socio-economic impacts and the risk-benefit assessment. She then considered whether in the problem formulation step, stakeholders should be involved in framing the problem and, if so, which stakeholders and what kind of involvement. As one answer to these questions, she reviewed the results of an international Delphi Study that asked if key stakeholders agreed with the new assessment approach regarding the question whether the existing system of food risk governance should be improved. The study reported 78% agreement among EU participants but 94% agreement among international (non-EU) stakeholders, suggesting differences even between these two groups. On the issue of improving communication between risk assessors and policy makers, she noted that presentations must be comprehensible, understandable, and credible. The applicability to public policy decision making must be clearly stated, assumptions should be described, and

#### Figure 4. Questions for the Communicating Scientific Information Breakout Session

- The link between technical expressions of risk resulting from health and environmental assessments may only tenuously link to health and environmental policy objectives. How can this link be made stronger?
- It is increasingly argued that assessment of both the risks and benefits associated with an event or activity is required input for decision making. How should risks and benefits of an event or activity be communicated to all end-users, e.g., the policy community or the general public?
- How should multi-criteria assessments (i.e., assessments incorporating socio-economic and ethical risk-benefit assessments as well as health and environmental impacts) be communicated? What metrics are needed as a basis for this communication?
- If transparency associated with risk analysis is to be increased, it is important that all factors influencing a decision are communicated. How can risk-benefit metrics be communicated in order to make decision making explicit, rather than an implicit risk management activity as is the case at present?
- What methods are available to target information to the needs of specific population groups?



the conclusions should be relevant to the specific risk management policy framework. She also discussed risk-benefit communication with consumers and, using the risks and benefits of fish consumption as an example, questioned whether the general public can understand the complex communication issues involved in evaluating both perspectives. She concluded by noting that a range of methods are available to quantify risks and benefits for issues regarding health, the environment, and socio-economic impacts. The questions include whether these methods are what is needed for risk assessment, how to improve transparency in risk governance, and how to optimize communications among risk assessors, policy makers, and the public.

The presentation by the next speaker, Donald Braman from George Washington University Law School, asked whether science communication can be fixed. He began by discussing two models of communication. The first, the rational cognition model, is based on the premise that information and education lead to increased understanding and to more accurate risk perception. In the cultural cognition model, information influences risk perception, but the values of individuals can affect their exposure to information because they can select information and then that process affects their perception of risk. For example, one can choose Fox News or MSNBC depending on which channel is providing information that is more appealing based on shared values. He went on to discuss nanotechnology as an example and noted that people who have an understanding and a familiarity with nanotechnology tend to have perceptions of lower risks and increased benefits compared to those who are unfamiliar with nanotechnology. He also commented that values shape perceptions and that people tend to trust others who share their values. However, people can switch their line of thinking if an expert source who presents a different perspective is trustworthy and knowledgeable. He concluded by proposing two strategies for improving science communication that included being aware of culturally antagonistic framings and finding cultural allies to vouch for the information.

Silke Gabbert from Wageningen University who spoke next on a value-of-information (VOI) analysis for sequential testing of chemicals opened her presentation by reviewing the economics of testing. She noted that use of a chemical can yield both benefits and disadvantages and that trade-offs usually exist between these two outcomes. However, information about a substance's potential for damage has value because it can trigger decision making about control actions for use of the chemical that can maximize its benefits. She went on to discuss a Bayesian VOI model of sequential testing in which a

test sequence that includes chance nodes and decision nodes is used to generate evidence in a step-wise fashion. At every decision node, an intermediate decision is made whether to stop or to continue testing. The VOI value is positive if information from testing triggers a risk management action that differs from the action selected with prior information. The best place to start the sequence is with the test that has the highest "savings potential" throughout the sequence; a test has savings potential if the evidence gained from this test saves a subsequent test and can be performed at lower cost than a subsequent test. She concluded that VOI analysis for toxicity testing must be designed for the specific set



Communicating Scientific Information breakout group participants.



of endpoints and for the specific substance. “Filling” a VOI model is an interdisciplinary effort that should involve toxicologists, ecotoxicologists, social scientists, statisticians, and risk assessors from industry and regulatory agencies.

Richard Belzer from Regulatory Checkbook continued in this topic area with his presentation on a VOI approach to risk benefit analysis. He commented that he viewed the precautionary principle as risk aversion due to uncertainty and noted that precautionary default risk assessment is a precautionary approach rather than conservative approach. He stated that



some scientific uncertainty can be reduced or eliminated by research but, if the research does not reduce uncertainty, it cannot reduce precaution in risk assessment or support risk management. He then proposed a path forward that included an evaluation of hypothesis-testing research based on pre-defined outcomes in which the hypothesis is refuted or not refuted but is a process that allows for well-defined surprises. His proposal also included establishing and executing durable prior agreements that are predicable, enforceable, and transparent and that are strictly limited to science. These durable prior agreements would establish beforehand the quality requirements for the data collection and the information and for the statistical methods and scientific inferences to be used. The process requirements would include open access to all data and models, participation in the science by all willing stakeholders, independent external validation, and the results produced would be legally enforceable. He concluded that the process should focus on independence by decision makers and an absence of interference from outside influences.

The next speaker, Melanie Bausen from BASF, presented an industry perspective on what information decision makers need to evaluate chemicals. She began her presentation by noting that in today’s world of global product flows, problems related to product safety and chemical safety extend beyond the country of product origin. She noted that although the amount of available information on chemicals has increased, trust and confidence in the safety of chemicals has not. Programs such as REACH generate extensive chemical information that is communicated between industry and regulators, but communication about the results of this information gathering to consumers is lacking. A key question is whether it is possible to increase consumer confidence through improved communication and she proposed a number of steps to achieve this end. These steps included transparency and widely sharing relevant information with all stakeholders as well as having consumers as an equal partner in the process. She suggested that the dangers of incomplete understanding of results need to be considered in cases where information may be presented either in an overly complicated or too simplistic manner. In addition, if information is to be useful to consumers, a balance of risk and benefit should be presented that addresses how this information may apply to consumers in their homes and their daily use of products. She also suggested acknowledging the uncertainties in current information and understanding what level of residual risk is acceptable to consumers. Communication must be continuous and proactive and provide sufficient information to help consumers make informed risk-benefit decisions. She noted that the chemical industry’s Global Product Strategy is a program that aligns with the goals of these proposed steps. In conclusion, she commented that risk communication should be linked to the benefits of the chemicals and products in daily life and that the benefits should outweigh the risks.



The final speaker for this afternoon session was Pertti Hakkinen from the U.S. National Institutes of Health, National Library of Medicine (NLM) who discussed the environmental health and toxicology resources at the NLM for risk assessment and risk management. He provided a brief overview of the variety of the online resources that are freely available from the NLM, which is the world's largest biomedical library. They included resources for environmental health and toxicology (TOXNET), chemical information (ChemIDplus), hazardous substances (HSDB), toxicity estimates (ITER), bibliographic databases (TOXLINE), and household products (Household Products database<sup>®</sup>). He went on to describe several teaching tools that are also available through the NLM, such as Tox Town<sup>®</sup>, an interactive guide to commonly encountered toxic substances, and ToxMystery<sup>™</sup>, a resource for children, parents, and teachers to learn about household chemical hazards. He also reviewed several enhancements in progress or under discussion at the NLM, such as providing access to the Comparative Toxicogenomics Database that links information about chemicals, genes, and diseases. In closing, he encouraged attendees to visit the NLM site and to review the variety of available resources.

*Day 2: Developing a Framework for Research: How Scientific Information Exchange Can Better Meet the Needs of Society*



Richard Shepherd from the University of Surrey was the first speaker on the second day of this breakout session and he discussed deliberate stakeholder engagement. He began his presentation by commenting that quantitative risk assessment is an expert model of risk and is very different from the way the public views risk. He noted that problems exist both in communication of risk to the public and in their confidence in the management of risk; recent examples include genetically modified organisms and mad cow disease. He stated that communicating risk to the public

should comprise several elements. They include getting the numbers right, explaining the numbers clearly, and, if possible, in a context relevant to their previous experience, as well as valuing the public and treating them as partners. He then reviewed the RELU-RISK project with its goal to investigate stakeholder participation in risk management. The project incorporated several participatory processes, such as stakeholder workshops, citizen juries, focus groups, and evaluated selected case studies. He reported that the pros and cons of the approach varied depending on the phase of the assessment with advantages in the early problem definition and evaluation stages and disadvantages in the risk assessment phase. For novel or major issues, assessments can benefit from participation, but limited time for this process is likely in crises situations. Each stage needs to include open discussion to air alternate views and structured discussion to develop consensus; consensus is nice but not essential. He concluded by stating that to maximize trust and credibility, all phases of the project must be transparent, documented, and open to independent review.



The next presentation by Madeleine Laffont from Cefic provided an industry perspective on stakeholder dialogues and asked whether or not they were meeting the needs of society. She listed several reasons why the chemical industry engages in stakeholder dialogues. First, she noted that they are required for transparency as part of Responsible Care® but that they can also enhance industry's reputation and can help the public understand the differences between industries and companies. Furthermore, they provide a venue to inform about research agendas and are useful for obtaining feedback. Involvement in dialogues also ensures that stakeholder concerns and aspirations are understood and that they are considered in decision making. They also provide an opportunity to collaborate with stakeholders on certain aspects of decision making. She then discussed stakeholder dialogues initiated by industry on four topics, including nanotechnology, workability of chemicals legislation, substitution/product bans, and climate change. The lessons learned include that stakeholder dialogue is not a public relations exercise and listening is important. The process must start early, be open and transparent, and the objectives must be clearly stated at the beginning to ensure internal alignment and realistic expectations from all parties. Projects should be focused and framed clearly with failures viewed as opportunities to learn. She noted that these dialogues have clear benefits to industry by increasing understanding of stakeholder opinions. She concluded by stating that stakeholder dialogues can meet society's needs by increasing confidence in the idea that the system can ensure safe products. The dialogues can provide objective information to make informed choices, provide input, and draw out opinions. Stakeholder dialogues can help by providing objective information and demonstrating that industry is one player in a team of information providers.

The final speaker for the morning session was Arnout Fischer from Wageningen University who discussed the topic of making social and natural sciences meet to address the challenges of predicting societal response to nanotechnology. He noted that nanotechnology is the latest in a series of technologies that has moved from the laboratory into society and that the time for such transition is becoming increasingly shorter. Societal response has previously impacted the fate of several technologies, most notably genetic modification in the EU, nuclear power in several countries, and food irradiation. To predict how nanotechnology will likely be accepted, insight is needed into the societal response to new technologies as well as assurances that societal values will be implemented in the early products. He conducted a literature review to investigate bringing nanotechnology to society looking at current approaches to predict societal response to new technologies, current knowledge on societal response towards nanotechnology, and the potential for collaboration between natural and social sciences. He found that there were no established structures for collaborations and that the problems included fundamental differences between social science and natural science, problems with understanding mutual jargon, a lack of mutual respect between the disciplines, a lack of organized collaborations, and an absence of opportunities for inter-





disciplinary research and training. Natural and social science collaborations can be successful if the scientists capitalize on opportunities and eliminate potential obstacles. He proposed two complementary approaches that include interactions between the two scientific disciplines to develop risk management for nanotechnology applications that are societally desirable and social science research to develop comprehensive empirically validated models about consumer behavior and their responses.

### *Discussion and Gap Analysis*

Lynn Frewer closed this breakout session by leading a discussion about the outcomes as well as conducting a gap analysis to formulate directions forward. To communicate effectively, she emphasized the importance of recognizing and understanding different cultural beliefs as well as different forms of communication. These considerations are important to identify real concerns as well as to overcome potential communication barriers. She suggested using a scenario approach to consider the different approaches used by scientists, government, industry, and stakeholders to work through the process. One recommendation discussed by participants was setting up approaches to integrate VOI and other



decision analysis tools into existing testing strategies. A tool box of decision analysis tools could be available for various specific problems; such tools could help research be more responsive to the decision information needs and to problem solving. To ensure purpose driven research, the approaches for interpreting the range of data results and translating them into decisions should be decided before collecting the results.

A question was raised about how best to communicate with consumers about chemicals and products and answer their questions. Some

aspects for consideration included the consumers' information needs, the content of risk-benefit information, and the best format for delivering and receiving the information, ideally in the form of a template or tool box. Other aspects for consideration were what authoritative resources, such as academia, industry, and government, would be available and the best ways to compile and disseminate the results to the different user or age groups.

One suggestion was to investigate how policy makers use information and generate new information, perhaps by applying a VOI approach. Another approach would be to evaluate how company research managers make decisions, perhaps through simulations that mimic decision making by providing information, getting stakeholder involvement, and seeing what they use. Another idea was to investigate expert models for designing user-centered approaches, such as web portals, that facilitate information access and how information is organized. An additional proposal was to replicate methodologies for engaging different projects at the community level in a handful of countries to develop a method that is culturally sensitive.



With regard to problems with information quality, such as statistical significance and excess precision, research is needed to understand what is meaningful and precision appropriate for the needs of decision makers. Another suggestion was development and testing of a unifying model that would apply available information about perception in a way that is useful for industry to understand social reactions to new technologies.

A closing suggestion was to encourage collaborations between natural and social sciences, perhaps around a specific topic to generate interest, perhaps with an offer of money to encourage such collaborations. Another suggestion was to train people who are both natural and social scientists as ambassadors between these areas and to encourage inter-disciplinary careers. Participants agreed that better ways of communicating uncertainty are needed. Integrating studies of human behavior with exposure assessment could be a useful approach because exposure science could benefit from the social sciences.

#### 4.0 Plenary Session III – Actualizing Innovation

The closing plenary session provided an opportunity for rapporteurs from each of the breakout sessions to summarize the presentations and discussions in each of the sessions, as presented in greater detail in the previous section. The rapporteurs were followed by two plenary speakers who were charged with discussing paths forward for integrating innovations in exposure science and toxicity testing. Jonathan Goodman from the University of Cambridge, the first speaker for this session, began by noting that his objective was to present a chemist's view of toxicology and to consider how these two scientific disciplines can better interface. His questions included:

- What limits our understanding of chemistry?
- What overlap exists between chemical and toxicological questions?
- Is chemistry good enough to solve toxicological questions?
- Can toxicological questions be phrased in ways chemists can understand?

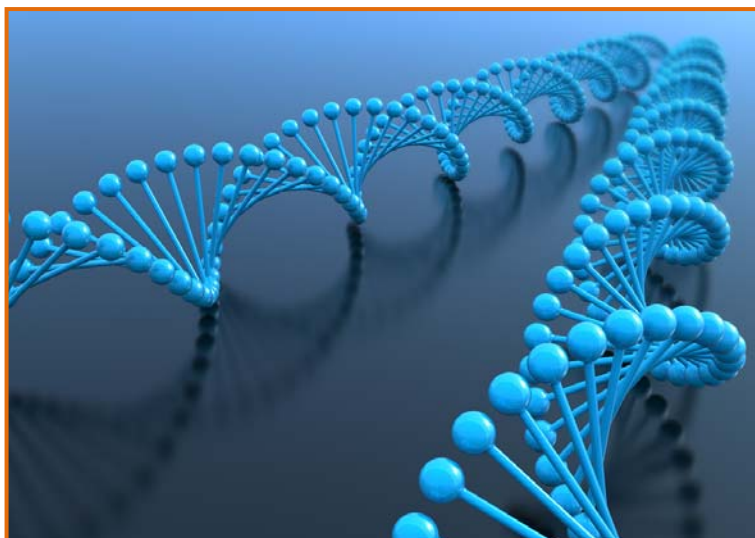
As an example of the importance of mutual understanding, he noted that the molecular acronym TCE that might be used by a toxicologist could suggest three different compounds to chemists, trichloroethylene, tetracyanoethylene, and trichloroethane. Using caffeine as another example, he observed that the physical and chemical properties listed for this compound differ in the literature for the two fields. He then reviewed a challenge that he had to calculate the solubility of 32 different chemicals using a database of 100 reliable measurements. The outcome was that the literature data on solubility was not good and that actual measurements of solubility further identified the difficulty in finding one correct solubility value. He concluded by noting that



Workshop participants tour the Indoortron laboratory at JRC following the workshop.



molecules have specific structures and that each structure can provide much valuable information. He thought that chemistry could help solve toxicological questions but that the questions must be presented in a way that chemists can understand. Integration of data from the two fields is important, and useful tools are now available. Such tools will become increasingly important to improve our understanding of chemicals and to enhance the field of toxicology.



The final plenary speaker for the meeting was Thomas McKone from the University of California, Berkeley, who spoke on the topic of stressors, targets, space and time: a science-based exposure narrative for impact management. He commented that stressors are numerous and they can include chemicals as well as physical and biological agents. The targets for these stressors can vary from individuals, populations, and communities to ecosystems and down to the tissue and cell levels. Importantly, space and time are critically linked to both stressors and targets in ways that can provide insights on diseases, their damage, and their costs. He defined the exposome as a lifetime narrative of human exposures to a full portfolio of stressors and described how interactions between stressors and targets at any point in time determine the exposure narrative. The challenges for



building an exposure narrative include exogenous factors that contribute to variable susceptibility as well as the contribution of multiple stressors. He noted that exposure science has predominantly been a descriptive science while its future is hypothesis-based research that merges models and data. He also noted that internal dose is becoming a more important metric as the effects of biokinetics in the body are increasingly understood. A current initiative for building the exposure narrative he described is a project to develop an exposure ontology that addresses data gaps among stressors, targets, and disease. As for future directions, he proposed weaving together the elements of exposure science with exposure biology, environmental monitoring, and disease surveillance, as well as relevant exposure models and statistical tools. He proposed building a comprehensive and reliable exposure narrative, the type of narrative that would be encoded in the exposome if such an entity existed as an analog to the genome. He emphasized the importance of research to understand how the mutual occurrence of stressor, target, space, and time determine a level of organization and detail that must be captured to understand disease burden and other impacts. Finally, case studies should be developed to demonstrate the value of melding models, environmental data, and biomarker data.



## 5.0 Workshop Summary

The overarching theme for this workshop was integrating developments in exposure science and toxicology to advance knowledge-based decision making about the safety of chemicals. A key consideration for this workshop was applying an integrated approach to the design, evaluation, and health risk management of chemicals. This workshop also considered what research is needed to improve communication between scientists and decision makers, and with stakeholders and end-users, including the public, to develop better chemical management policies and practices.

Key outcomes from this workshop include the following:

- Advances in molecular technologies are enabling environmental epidemiology and toxicology to identify the exposure-effect relationship at the cellular, organismal, and population levels.
- The success of these approaches hinges on the availability of biologically-relevant exposure information that is rapidly evolving from improved measurement technologies, more targeted biomonitoring studies, and applications of advanced informatics and computational tools.
- The exposome, defined as a lifetime of human environmental exposures including lifestyle factors, was highlighted as a possible framework for guiding developments in exposure science.
- Stem cells offer great potential for the development of *in vitro* toxicity models that are relevant to effects that can occur in humans; similarly, new imaging methods offer innovative approaches to understand mechanisms of toxicity in *in vitro* models.
- Computational models are becoming increasingly sophisticated and advanced both in the analysis of 'omics' data, such as high throughput methods, as well as in their predictive capabilities, such as for biological system interactions and QSAR modelling.
- New informational tools, including the ToxPi and CVST, can incorporate and transform multiple types of chemical information into visual formats that facilitate chemical prioritization and identification of areas for additional toxicity testing.
- VOI methods and other decision analysis tools provide an approach for identifying those test protocols that offer the best value in terms of resource allocation.
- Effective communication about chemicals must include both risk and benefit information so that all shareholders, including the public, are fully informed.
- Risk characterization is an analytical, deliberative, and decision-driven process; successful characterization of risk for chemicals requires getting the science and the participation right as well as getting the right science and the right participation.
- Stakeholders must be part of the risk assessment process to improve credibility and the utility of the results; input, dialogue, and engagement are more important than consensus among all stakeholders.



Workshop attendees visit the JRC after the workshop.



Undoubtedly, new cellular, analytical, and computational methods, alone and in combination, provide exciting new approaches for chemical evaluation and integrated testing strategies. However, a significant confluence of will and resources will be required to implement these strategies and to create the requisite paradigm shift in chemical safety assessments. Without a collective commitment to build capacity and to create a strategic shift, the advancements in science discussed at this workshop are likely to outpace the decision making, regulatory and policy mechanisms that need to adopt the new science.

This JRC & ICCA-LRI workshop provided an international forum to foster interactions among researchers and stakeholders, stimulate discussions for improving the scientific basis for policymaking, and support consensus building that can advance the risk assessment process for chemicals. This and the previous ICCA-LRI workshops demonstrate the value of participatory and collaborative development of the science relevant to directly addressing many of the complex scientific and regulatory challenges for effective chemical management policies. Additional information about the ICCA-LRI, its research programs, publications, future workshops, and other activities can be found at our Web site ([www.icca-chem.org/LRI](http://www.icca-chem.org/LRI)).



## References

- National Research Council. 2008. Science and Decisions: Advancing Risk Assessment. The National Academies Press, Washington, DC.
- National Research Council. 2007. Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy. The National Academies Press, Washington, DC.
- National Research Council. 1996. Understanding Risk - Informing Decisions in a Democratic Society. The National Academies Press, Washington, DC.
- National Research Council. 1983. Risk Assessment in the Federal Government: Managing the Process. The National Academies Press, Washington, DC.
- Wild CP. 2005. Complementing the genome with an “exposome”: The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiology, Biomarkers & Prevention* 14:1847-1850.

[This page left blank intentionally]



## Appendix A: Participant Affiliations

American Chemistry Council  
BASF SE  
Bayer AG  
Bayer CropScience AG  
Bayer MaterialScience  
Bayer S.A.S.  
Beyond Benign  
BioMed zet Life Science GmbH  
Biovator AB  
Ca' Foscari University of Venice  
Cefic (European Chemical Industry Council)  
Cellartis AB  
Centre for Chemical Substances and Preparations,  
Slovakia  
Chelab srl  
Chemical Watch  
Clemson University  
Domostyle SRL  
DuPont  
DuPont Coordination Center  
DuPont Engineering  
Durham University  
European Centre for Ecotoxicology and Toxicology of  
Chemicals  
European Chemicals Agency  
EggCentris  
Emilia-Romagna EPA  
Emory University  
ETH Zürich  
European Chemicals Agency  
European Coalition to End Animal Experiments  
European Commission - Joint Research Centre  
ExxonMobil Biomedical Sciences, Inc.  
ExxonMobil Petroleum & Chemical  
F.Hoffmann-La Roche Ltd  
Federal Environment Agency  
Federchimica - Centro Reach  
General Directorate of Health  
George Washington University Law School  
Henkel AG & Co. KGaA  
Humane Society of the United States  
ICF International  
Imperial College London  
INFOTOX  
Institut National de la Santé et de la Recherche  
Médicale, France  
Institute for the Environment  
Istituto Mario Negri  
Istituto Nazionale per l'Assicurazione, Italy  
Japan Chemical Industry Association  
Johns Hopkins University  
Lamberti  
Landesuntersuchungsamt  
Lion Corporation  
Maugeri Foundation, Scientific Institute of Pavia  
Max Planck Institute for Molecular Genetics  
Medical Research Council  
National Hellenic Research Foundation  
National Institute for Health and Welfare, Finland  
National Institute of Environmental Health  
Sciences  
National Research Council  
NovaLeads  
Procter & Gamble  
Pt. Ravishanakar Shukla University  
Regulatory Checkbook  
National Institute for Public Health and the  
Environment, The Netherlands  
Roche  
Rutgers University  
Shell International bv  
Stanford University  
Summit Toxicology  
The Dow Chemical Company  
The Hamner Institutes for Health Sciences  
TNO Quality of Life  
Tokushima Bunri University  
U.S. Environmental Protection Agency  
U.S. National Institutes of Health  
Unilever  
United Nations Platform for Action Committee  
University of Aarhus  
University of California  
University of Cambridge  
University of Insubria - Varese & Como  
University of Milano Bicocca  
University of Ottawa  
University of Surrey  
University of Valladolid  
VITO  
Wageningen University

[This page left blank intentionally]



## Appendix B: Workshop Program

Wednesday, 16 June 2010

### Registration

07.00 – 08.00

### Hosts' Welcome

08.00 – 08.15

- Maurice Whelan, European Commission, Joint Research Centre, Italy
- Jan Mostowy, Bayer Corporation, USA

### Plenary Session I: Integrating Science for Chemical Safety Assessment

08.15 – 10.00

**Session Chair:** Annette Guiseppi-Elie, DuPont, USA

#### Workshop objectives and expected outcomes

- Annette Guiseppi-Elie, DuPont, USA

#### Risk assessment challenges concerning the European Union legislative framework

- Maurice Whelan, European Commission, Joint Research Centre, Italy

#### Integrating science for improved chemical safety assessments – myth or reality?

- Alan Boobis, Imperial College, UK

#### Risk communication and decision making

- Caron Chess, Rutgers University, USA

### Morning Break

10.00 – 10.30

*Winter Garden*

### Plenary Session II: Setting the Stage for the Breakout Sessions

10.30 – 13.00

**Session Chair:** Maurice Whelan, European Commission, Joint Research Centre, Italy

#### Thoughts on exposure science for health management

- Matti Jantunen, National Public Health Institute's Department of Environmental Health, Finland

#### Emerging technologies that enhance the performance of cell-based in vitro tests and enable improved predictive toxicity

- Stefan Przyborski, Relnervate, UK

#### Biological susceptibility and cellular elasticity – Robustness and vulnerability of embryos to toxicants

- David Epel, Stanford University, USA

#### A mechanistic re-definition of adverse effects – Linking in vitro toxicity testing results to risk assessment

- Mel Andersen, The Hamner Institutes for Health Sciences, USA

#### Integrated tools for the next generation of risk assessment – challenges and possibilities

- Bette Meek, Health Canada & University of Ottawa, Canada



**Lunch**

**13.00 – 14.00**

**Breakout Session 1: Exposure Science**

**14.00 – 17.00**

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

**Session Chair:** Elaine Cohen Hubal, Environmental Protection Agency, USA

**Rapporteur:** Corinna Weinz, Bayer AG, Germany

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

**Day 1 Theme: Chemical evaluation for public health decisions**

**ExpoCast™: Exposure science for prioritization and toxicity testing**

- Elaine Cohen Hubal, Environmental Protection Agency, USA

**Incorporating exposure information into Toxicological Priority Index (ToxPi) for chemical prioritization**

- Sumit Gangwal, Environmental Protection Agency, USA

**The German human biomonitoring effort and the EU project COPHES – Contributions for a harmonized European human biomonitoring**

- Marike Kolossa-Gehring, Federal Environment Agency, Germany

**Modeling consumer exposures to environmental chemicals**

- Natalie von Götz, ETH Zurich, Switzerland

**A chemical screening visualization tool – Avoiding roadblocks on the route to commercialization**

- Mario Chen, DuPont, USA

**Green engineering – Steps for design towards sustainability**

- Juan García Serna, University of Valladolid, Spain

**Breakout Session 2: Toxicity Testing**

**14.00 – 17.00**

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

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

**Rapporteur:** Grace Patlewicz, DuPont, USA

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

**Innovative approaches to generating, integrating, and interpreting hazard data**

- Tim Gant, University of Leicester, UK

**Day 1 Theme: Emerging models for human-based toxicity testing**

**New scanning microscope technique for functional characterisation, manipulation, and monitoring of living stem cells**

- Julia Gorelik, Imperial College, UK

**Applications of hESC-derived hepatocytes in toxicity and ADME testing**

- Claudia McGinnis, Roche (Basel), Switzerland

**Stem cell-derived hepatocytes and their use in toxicology**

- Christiane Guillouzo, Université de Rennes, France



### Breakout Session 2: Toxicity Testing

14.00 – 17.00

**The effect of chemicals on the tissue-specific homing of T cells**

- Makoto Iwata, Tokushima Bunri University, Japan

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

**Cellular models for cytotoxicity and developmental toxicity analysis on human pluripotent stem cells**

- Mia Emgård, Cellartis, Sweden

### Breakout Session 3: Communicating Scientific Information

14.00 – 17.00

**Session Chair:** Lynn Frewer, Wageningen University, The Netherlands

**Rapporteur:** Melanie Bausen, BASF – The Chemical Company, Germany

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

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

#### Day 1 Theme: Addressing the nodes of disconnect

**Description of breakout session, charge to participants, and introduction to Social Impact Assessment (SIA)**

- Lynn Frewer, Wageningen University, The Netherlands

**Can science communication be fixed?**

- Donald Braman, George Washington University Law School, USA

**A value-of-information analysis for sequential testing**

- Silke Gabbert, Wageningen University, The Netherlands

**A value-of-information approach to risk-benefit analyses**

- Richard B. Belzer, Regulatory Checkbook, USA

**Communicating scientific information - Industry perspective**

- Melanie Bausen, BASF – The Chemical Company, Germany

**The activities of the U.S. National Library of Medicine to collect, organize, preserve, and disseminate current and emerging information in toxicology, exposure science, risk assessment, and risk management**

- Pertti Hakkinen, U.S. National Institutes of Health, National Library of Medicine, USA

### Reception and Poster Viewing

17.00 – 19.00

Group Dinner

19.00



Thursday, 17 June 2010

Registration

07.00 – 08.00

Breakout Session 1: Exposure Science

08.00 – 10.15

**Session Chair:** Elaine Cohen Hubal, Environmental Protection Agency, USA

**Rapporteur:** Corinna Weinz, Bayer AG, Germany

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

**Day 2 Theme: Integrating exposure and health sciences for better decisions**

**Use of 'omics' to characterize human exposure**

- Martyn Smith, University of California, Berkeley, USA

**High-throughput clinical metabolomics – Nutritional and environmental effects on human health**

- Dean Jones, Emory University, USA

**Advancing metabonomic techniques for assessing environmental effects on human health**

- Toby Athersuch, Imperial College, London, UK

**Exploring the potential of 'omics' technologies in population studies: The EnviroGenomarkers project**

- Soterios Kyrtopoulos, National Hellenic Research Foundation, Institute of Biological Research and Biotechnology, Greece

**Discussion and Collective Perspectives**

**Discussion Lead:** Peter Boogaard, Shell, The Netherlands

Breakout Session 2: Toxicity Testing

08.00 – 10.15

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

**Rapporteur:** Grace Patlewicz, DuPont, USA

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

**Day 2 Theme: Computational and integrative methods for predictive toxicology**

**Prediction in the face of uncertainty: A Monte Carlo strategy for systems biology of cancer treatment**

- Christoph Wierling, Max Plank Institute for Molecular Genetics, Germany

**Metabonomics for understanding mechanisms of toxicity and inter-individual response**

- Muireann Coen, Imperial College, UK

**The use of computational methods in regulatory decision making**

- Andrew Worth, European Commission, Joint Research Centre, Italy

**Endocrine disrupter and threshold effect: A case study**

- David Rouquié, Bayer Crop Science, France



### Breakout Session 2: Toxicity Testing

08.00 – 10.15

#### Computational toxicology - A (Q)SAR perspective

- Grace Patlewicz, DuPont, USA

#### Discussion and Collective Perspectives

**Discussion Lead:** Tim Gant, University of Leicester, UK

### Breakout Session 3: Communicating Scientific Information

08.00 – 10.15

**Session Chair:** Lynn Frewer, Wageningen University, The Netherlands

**Rapporteur:** Melanie Bausen, BASF – The Chemical Company, Germany

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

#### Day 2 Theme: Developing a framework for research: How scientific information exchange can better meet the needs of society

#### **Deliberate stakeholder engagement**

- Richard Shepherd, University of Surrey, UK

#### **Stakeholder dialogues: Industry perspective – Meeting the needs of society?**

- Madeleine Laffont, CEFIC aisbl (European Chemical Industry Council), Belgium

#### **Making social and natural sciences meet: The need and challenges for natural-social science in predicting societal response to nanotechnology**

- Arnout Fischer, Wageningen University, The Netherlands

#### Discussion and Gap Analysis

**Discussion Lead:** Lynn Frewer, Wageningen University, The Netherlands

### Morning Break

10.15 – 10.45

### Breakout Session Summaries

10.45 – 12.00

**Session Chair:** Richard D. Phillips, ExxonMobil, Belgium

#### Presentations

- **Exposure Science:** Corinna Weinz, Bayer AG, Germany
- **Toxicity Testing:** Grace Patlewicz, DuPont, USA
- **Communicating Scientific Information:** Melanie Bausen, BASF – The Chemical Company, Germany



**Plenary Session III: Actualizing Innovation**

12.00 – 12.50

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

**Computational chemistry and chemical informatics to develop and manage chemical information**

- Jonathan Goodman, University of Cambridge, UK

**Stressors, targets, space and time: A science-based exposure narrative for impact management**

- Tom McKone, University of California, Berkeley, USA

**Workshop Closing Remarks and Afternoon Programme**

12.50 – 13.00

- Maurice Whelan, European Commission, Joint Research Centre, Italy

Lunch

13.00 – 14.00

Tour of Joint Research Centre (JRC)

13.00 – 17.00

*Joint Research Centre, Ispra, Italy*

[This page left blank intentionally]



## Appendix C: List of Poster Presentations

	<b>First Author Affiliation</b>	<b>Presenter Affiliation</b>	<b>Abstract Title</b>
1	<b>Y. Adeleye</b> <i>Unilever, UK</i>	<b>Y. Adeleye</b> <i>Unilever, UK</i>	Identification of toxicity pathways of lung toxicity and applications to development of non-animal approaches for risk assessment
2	<b>H.K. Bahia</b> <i>University of Leicester, UK</i>	<b>T.W. Gant</b> <i>University of Leicester, UK</i>	Application of cardiomyocytes from mouse embryonic stem cells in understanding drug induced chemical toxicity
3	<b>E. Boriani</b> <i>Laboratory of Environmental Chemistry and Toxicology, Mario Negri Institute for Pharmacological Research, Italy</i>	<b>E. Benfenati</b> <i>Laboratory of Environmental Chemistry and Toxicology, Mario Negri Institute for Pharmacological Research, Italy</i>	ERICA: A multiparametric eco/toxicological risk index for assessment of environmental health and risk communication
4	<b>T. Borges</b> <i>Portuguese Toxicology Association and Environmental Health Division, Health Directorate-General, Portugal</i>	<b>T. Borges</b> <i>Portuguese Toxicology Association and Environmental Health Division, Health Directorate-General, Portugal</i>	Impact of REACH in Portugal: Results of the AP Tox survey
5	<b>E. Carney</b> <i>The Dow Chemical Company, USA</i>	<b>E. Carney</b> <i>The Dow Chemical Company, USA</i>	Near-term opportunities to apply new technologies to drive decision making within the chemical industry
6	<b>K. Choi</b> <i>The Hamner Institutes for Health Sciences, USA</i>	<b>H. Clewell</b> <i>The Hamner Institutes for Health Sciences, USA</i>	The <i>in vitro</i> metabolism of di (2-ethylhexyl) phthalate in rat and human and its anti-androgenic effects on Leydig cells
7	<b>H. Clewell</b> <i>The Hamner Institutes for Health Sciences, USA</i>	<b>H. Clewell</b> <i>The Hamner Institutes for Health Sciences, USA</i>	Research on <i>in vitro</i> to <i>in vivo</i> extrapolation (IVIVE) and reverse dosimetry
8	<b>Sandra Coecke</b> <i>European Commission, Joint Research Centre, Italy</i>	<b>Sandra Coecke</b> <i>European Commission, Joint Research Centre, Italy</i>	Multi-study validation trial for cytochrome P450 induction providing a reliable human-metabolic competent standard model or method using the human cryoHepaRG <sup>®</sup> cell line and cryopreserved human hepatocytes
9	<b>C. Correzzola</b> <i>INAIL D.P. Trento, Italy</i>	<b>C. Correzzola</b> <i>INAIL D.P. Trento, Italy</i>	Is density functional theory (DFT) a way to theoretical toxicology?
10	<b>R. Cortvrindt</b> <i>EggCentris, Belgium</i>	<b>R. Cortvrindt</b> <i>EggCentris, Belgium</i>	The <i>in vitro</i> test methods for reproductive toxicity: When to use?
11	<b>S. Derick</b> <i>Novaleads, France</i>	<b>C. Furger</b> <i>Novaleads</i>	Dequenching after photobleaching (DAP) assay: A new high-throughput live cell approach to measure DNA alteration



	<b>First Author Affiliation</b>	<b>Presenter Affiliation</b>	<b>Abstract Title</b>
12	<b>P. D'Ursi</b> <i>CNR-ITB, Italy</i>	<b>P. D'Ursi</b> <i>CNR-ITB, Italy</i>	Reverse molecular docking for the identification of protein targets and pathways of endocrine disruptor bisphenol A
13	<b>P.J. Hakkinen</b> <i>National Institutes of Health, National Library of Medicine, USA</i>	<b>P.J. Hakkinen</b> <i>National Institutes of Health, National Library of Medicine, USA</i>	The (U.S.) National Library of Medicine: Collecting, organising, preserving, and disseminating current and emerging information in toxicology, exposure science, and risk assessment
14	<b>S.M. Hays</b> <i>Summit Toxicology, LLP, USA</i>	<b>S.M. Hays</b> <i>Summit Toxicology, LLP, USA</i>	Consideration of "dose" in evaluation of ToxCast™ Data: Comparison of relative potencies of acetylcholinesterase inhibitors
15	<b>K. Mattsson</b> <i>Biovator AB, Sweden</i>	<b>K. Mattsson</b> <i>Biovator AB, Sweden</i>	Protein allergenicity: Experiences in the development of an in vitro assay for identifying protein allergens
16	<b>P. Price</b> <i>The Dow Chemical Company, USA</i>	<b>E. Carney</b> <i>The Dow Chemical Company, USA</i>	Characterising cumulative risk using the maximum-cumulative ratio (MCR)
17	<b>R.J. Safford</b> <i>Unilever, UK</i>	<b>C. Clapp</b> <i>Unilever, UK</i>	Refining the dermal sensitisation threshold: A TTC approach for allergic contact dermatitis
18	<b>D. Sarigiannis</b> <i>European Commission, Joint Research Centre, Italy</i>	<b>D. Sarigiannis</b> <i>European Commission, Joint Research Centre, Italy</i>	A computational framework for aggregate and cumulative exposure assessment
19	<b>R. Smolders</b> <i>VITO, Environmental Risks and Health Unit, Belgium</i>	<b>R. Smolders</b> <i>VITO, Environmental Risks and Health Unit, Belgium</i>	A new dawn for exposure assessment
20	<b>R. Thomas</b> <i>The Hamner Institutes for Health Sciences, USA</i>	<b>R. Thomas</b> <i>The Hamner Institutes for Health Sciences, USA</i>	Application of transcriptional benchmark dose values in quantitative cancer and noncancer risk assessment
21	<b>R. Thomas</b> <i>The Hamner Institutes for Health Sciences, USA</i>	<b>R. Thomas</b> <i>The Hamner Institutes for Health Sciences, USA</i>	Incorporating human dosimetry and exposure into high throughput in vitro toxicity screening
22	<b>M. Viau</b> <i>Institut National de la Santé et de la Recherche Médicale, France</i>	<b>M. Viau</b> <i>Institut National de la Santé et de la Recherche Médicale, France</i>	How to quantify toxicity and cancer risks after contamination with metals? Toward a "chemical" Sievert unit system?
23	<b>A. Zenié</b> <i>European Commission, Joint Research Centre, Italy</i>	<b>A. Zenié</b> <i>European Commission, Joint Research Centre, Italy</i>	European Exposure Factors (ExpoFactors) Sourcebook: Supporting risk and exposure assessment of European populations
24	<b>A. Zenié</b> <i>European Commission, Joint Research Centre, Italy</i>	<b>A. Zenié</b> <i>European Commission, Joint Research Centre, Italy</i>	Characterising and communicating qualitative uncertainty within risk and exposure assessments by using TUA