



**Navigating Obstacles Towards  
Modernizing Risk Assessment**

# **Workshop Summary Report**

**February 23 and 24, 2010**

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and International Trade Center**

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## List of Acronyms

ACC	American Chemistry Council
CBI	confidential business information
CDC	Centers for Disease Control and Prevention
CTD	comparative toxicogenomics database
DEHP	di(2-ethylhexyl) phthalate
EPA	U.S. Environmental Protection Agency
G x E	genes and environment
HTS	high-throughput screening
HuGE	human gene epidemiology
IRIS	Integrated Risk Information System
LOAEL	lowest observable adverse effect level
LRI	Long-Range Research Initiative
MTBE	methyl <i>tert</i> -butyl ether
NGO	non-governmental organization
NexGen	next generation (EPA risk assessment initiative)
NHANES	National Health and Nutrition Examination Study
NOAEL	no observable adverse effect level
NRC	National Research Council
PBPK	physiologically-based pharmacokinetic
PBT	persistent, bioaccumulative, and toxic
POD	points-of-departure
POP	persistent organic pollutant
QSAR	quantitative structure-activity relationship
RfD	reference dose
SETAC	Society of Environmental Toxicology and Chemistry
SST	Strategic Science Team (of the LRI)
STAR	Science to Achieve Results
TSCA	Toxic Substances Control Act
UNEP	United Nations Environment Programme

## Executive Summary

The Long-Range Research Initiative (LRI) of the American Chemistry Council (ACC) held a workshop, *Navigating Obstacles Towards Modernizing Risk Assessment*, on February 23 and 24, 2010 in Washington, DC. The impetus for this workshop was several recent reports published by the National Research Council (NRC) that contain numerous recommendations for improving risk assessment, as well as new initiatives by the U.S. Environmental Protection Agency (EPA) designed to increase the efficiency of risk assessment processes. Another element was emerging developments in 'omics' technologies and bioinformatics sciences; these new research areas promise exciting new data and



insights about chemicals and their effects that could improve regulatory decision making. More than 100 participants from government, academia, non-governmental organizations (NGOs), and industry attended this workshop to discuss opportunities and challenges presented by these recent events, and how best to modernize current practices in risk assessment.

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

- Risk assessment practices must be advanced so that they more efficiently and effectively protect public health. This effort will require scientific and policy input, as well as consensus among a variety of stakeholders, including academia, government, industry, and NGOs, as well as acceptance by the general public.
- Recent NRC reports provide numerous recommendations to significantly advance risk assessment; they include an approach that emphasizes planning and scoping in the initial assessment phase, decreased use of animals, use of new technologies, and consideration of the impacts of various risk management options and the associated costs. The NRC acknowledges that achieving these recommendations will take a substantial scientific effort over many years.
- The quality, quantity, and use of exposure assessment information must be increased to improve risk assessment; advancements in exposure models are needed to support these efforts.
- New approaches that address the effects of cumulative exposures to multiple substances and multiple stressors, particularly for susceptible populations such as children and the elderly, are needed to understand the health effects from everyday exposure conditions.
- Risk assessment practices that incorporate the use of new technologies, such as EPA's NexGen, and innovative approaches that consider exposures to chemical mixtures, including use of ecological models, are examples of ongoing efforts to modernize risk assessment.
- New technologies and bioinformatic sciences offer promising approaches to advance risk assessment and increase its efficiency; however, interpreting these new data and identifying approaches to effectively incorporate the data into risk assessment are current challenges.
- Increased transparency and communication in risk assessment and risk management processes must be part of a reinvigorated risk assessment that incorporates pragmatic and practical approaches and facilitates, rather than hinders, decision making.

## I. Introduction

Recent events have provided a compelling case for modernizing chemical risk assessment and were an impetus for convening this workshop, *Navigating Obstacles Towards Modernizing Risk Assessment*. These events included a series of reports from the NRC (2009; 2008; 2007a; 2007b; 2007c) that form a critical basis for rethinking how risk assessment is done and provide numerous and varied recommendations for advancing the science. Other key drivers included initiatives by the EPA to increase the efficiency of the risk assessment process and the use of tools and data emerging from 'omics' technologies and bioinformatic sciences that could potentially improve regulatory decision making.

Modernizing chemical risk assessment presents numerous challenges. The presentations and discussions during this workshop, which was sponsored by the LRI of the ACC, identified a number of current obstacles toward achieving these objectives. Workshop participants agreed that the current risk assessment practices are too costly, too slow, use too many animals, and evaluate too few chemicals. As an example, only several hundred substances among the thousands in commerce currently have values listed in the EPA's Integrated Risk Information System (IRIS) database. Participants also agreed that the new 'omics' technologies and bioinformatic sciences offer great promise for advancing risk assessment and increasing its efficiency; however, interpreting the data obtained from these approaches and appropriately incorporating the data into risk assessments remain as current challenges. It is yet to be determined how current initiatives to reform the Toxic Substances Control Act (TSCA), which was enacted more than 30 years ago in 1976, will include these new technologies. An overall objective of the workshop was to identify and discuss current obstacles for advancing risk assessment and to evaluate the innovative approaches and tools that can address these obstacles.



This one and one-half day workshop brought together more than 100 participants from governmental agencies, industry, academia, and NGOs to discuss the challenges and opportunities for modernizing chemical risk assessment. A navigational theme was selected for this workshop because advancing



risk assessment, like any journey, will include encounters with anticipated and unanticipated obstacles. The challenge is to recognize the obstacles, determine how best to manage them, and then identify new paths forward. The workshop format included a series of plenary presentations on several topics interjected with panel discussions to provide speakers and participants an opportunity to present their perspectives. A series of questions developed prior to the workshop served as starting points for the three panel discussions, which included both the plenary speakers and invited speakers.

## II. Welcome Remarks

The important question of how to capitalize on the new technologies and scientific advances and achieve the highest standard in regulatory policy for chemical management was a theme for the introductory remarks by Cal Dooley, Chief Executive Officer of the ACC. He noted that broad-based participation by a variety of stakeholders, including industry, researchers, NGOs, and regulatory agencies, should be an important objective for the current initiatives to reform TSCA because no one is well served if consumers lack confidence in the safety of a product. He commented that the EPA should prioritize chemicals for safe use determinations and identify those with increased levels of concern for safety that may require more comprehensive risk and safety assessments. He noted the importance of continuing the dialog among stakeholders so that a policy can be developed, passed by Congress, signed into law, and become the gold standard for chemical management. In closing, he stated that the chemical industry is committed to constructive engagement in the development of these policies, and that his vision is a standard and a system that serve the needs of companies, consumers, and the general public.

Welcome remarks were also provided by Janet Mostowy from Bayer MaterialScience, who is the chair of LRI's Strategic Science Team (SST). The SST, which is responsible for managing the LRI, includes senior scientists and managers from ACC member companies, academia, NGOs, and governmental agencies. She provided an overview of LRI's current research strategy that comprises three research areas—new technologies, exposure science, and susceptible populations—with an overall focus on modernizing chemical risk assessment. She noted that this workshop was an implementation of the outreach component of the research strategy designed to promote interactions between researchers and stakeholders, stimulate discussions that can improve the scientific basis for policymaking, and support consensus building to address the important issue of advancing risk assessment.



## III. Setting a Course

The goal of the first plenary session was to provide an overview of the importance of modernizing risk assessment and to discuss how best to proceed from science to decisions and to move beyond potential obstacles.

The first speaker, Paul Gilman from Covanta Energy Corporation, commented that the EPA had accomplished much in the area of risk assessment since its 1983 publication of *Risk Assessment in the Federal Government: Managing the Process* (NRC 1983), informally known as “The Red Book.” He also encouraged revisiting the recommendations provided in the 2004 EPA Staff Paper, *An Examination of Risk Assessment Principles and Practice* (EPA 2004). He recommended developing specific datasets that can more accurately assess potential risks; improving communication about the use of data, assumptions, and defaults; and focusing on ways to address uncertainty. He emphasized the critical need for transparency in both risk assessment and risk management practices. He also

noted the importance of developing approaches to address the effects of cumulative exposures to multiple substances and multiple stressors, particularly for susceptible populations, such as children and the elderly, who may be at increased risk for adverse health effects. In addition, he encouraged the use of multiple resources to define and pursue the broader agenda of modernizing risk assessment. These resources include engaging the research staffs from a variety of areas within the EPA; governmental funding tools, such as the EPA's Science to Achieve Results (STAR) grants program; cooperative research agreements; independent funding sources; and engagement of professional societies, NGOs, and foundations.

#### IV. Perspectives on Directions Forward

This session provided the opportunity for representatives from three different stakeholder groups, including the federal government, an NGO, and the chemical industry, to share their perspectives on how to improve risk assessment and facilitate better decision making.

The first speaker, Peter Preuss from the EPA, discussed current and future challenges for human health risk assessment. He stated that risk assessment has been, and will continue to be, the fundamental basis for decision making within the EPA. However, because of acknowledged drawbacks in the current risk assessment processes, as previously described, he proposed moving to the next generation (NexGen) of risk assessment. This approach would incorporate use of the new 'omics' and other analytical technologies and benefit from an increased understanding of the contribution of gene-environment interactions. NexGen would include a high-priority list of chemicals and a streamlined



process that would broaden the scope of risk assessments so that more information could be incorporated into each assessment. In Tier 1 of the proposed NexGen approach, thousands of chemicals would be screened and prioritized using a variety of approaches, including high-throughput screening (HTS), virtual biological systems, and quantitative structure-activity relationships (QSARs). Based on this prioritization process, hundreds of chemicals would likely be selected for Tier 2 assessments; generally, these chemicals would have limited hazard and exposure data and these assessments would include science-based defaults and upper confidence limit risk estimates.

It is anticipated that dozens of chemicals would be categorized as potential high-hazard or high-exposure substances and be selected to undergo Tier 3 assessments. Such assessments would include a review of all policy-relevant data, new technologies data, and best estimates from risk and uncertainty analyses. The overall vision is that the development and evolution of NexGen will be an iterative process that would include workshops, case studies, and cumulative risk assessment approaches as well as other assessment strategies as part of its ongoing refinement and improvement. The speaker cautioned that it may be 10 years or more before human health risk assessment can rely on these new advances in science, but it is important to begin now.

The next speaker, Richard Denison from the Environmental Defense Fund, opened his presentation by discussing the differences between hazard and exposure and stating that knowledge about both is



essential for developing meaningful human health risk assessments. He commented that hazard is an inherent property of a substance, whereas the assessment of exposure to a substance depends on several factors, including place, use, and time. In the real world, exposures are affected by these spatial and temporal factors, as well as sources, pathways, and routes of exposure for the exposed individual; however, most exposure assessment data represent a snapshot in time. He expressed concerns about the credibility and transparency of current risk assessment processes, and noted that the current lack of quality exposure data is a weak link. He also expressed concerns that claims of confidential business information (CBI) limit access to pertinent information for those in the supply chain, including the general public. He provided examples of early estimates of low or limited exposures to some chemicals that later proved to be incorrect as more information became available. He ended his point by commenting that overconfidence in the currently available exposure data likely exists. To advance risk assessment, he noted that it will be essential to increase both the quality and quantity of exposure information as well as transparency in the risk assessment processes. He concluded his presentation by listing several current needs for exposure policy and practice. They include an international consensus on standards for exposure assessment and data collection, a process for independent review of data by outside experts, approaches that account for the variable nature of exposure, and improved access to and review of exposure data.

The third speaker, Richard Becker from ACC, began his presentation with a review of ACC's *10 Principles for Modernizing TSCA* (ACC 2009) that outlines the various and shared responsibilities of the chemical industry and the EPA designed to insure that chemicals are safe for their intended use by the general public. He suggested that within a modernized TSCA, the legislation that provides the EPA with its regulatory authority, both relevant toxicity data and information derived from computational models, such as 'omics' approaches including HTS and QSARs, should be used in priority setting and hazard and risk evaluation for risk assessment. An overall objective of risk assessment would be to include data from all sources of high-quality scientific research—independent of funding source or affiliation—and to review it objectively and comprehensively, weight it appropriately, and develop a robust, biologically plausible understanding of the potential risks from exposure. He noted that the new technologies offer significant opportunities to better understand the tipping point between adaptive responses and adverse effects, as well as the underlying events in cells and tissues that lead to toxicity. Future research directions include differentiating the effects of closely related compounds, grouping compounds into categories based on biological profiling, and evaluating toxicity pathways at the low end of the dose-response curve.



## V. Advancing Risk Assessment Considerations for Public Health Protection

The presentations in this session considered risk assessment within the context of its role to protect public health.

The first speaker, Joseph Rodericks from ENVIRON International Corporation, focused on the findings in the 2009 NRC report, *Science and Decisions: Advancing Risk Assessment* (NRC 2009), informally known as “The Silver Book,” and the framework it presents for modernizing human health risk assessment. He noted that this new framework differs from that presented in “The Red Book” (NRC 1983), which focused on the initial and final phases of the risk assessment process. In “The Silver Book,” greater emphasis is placed on the first phase of problem formulation and scoping; its goal is early and thorough planning that tailors the assessment’s level and complexity to the demands of the problem and considers the assessment’s costs and technical feasibility. He commented that more and better exposure assessment information should be the first priority to improve risk assessment; if good measurements of exposure are available, this information can guide what level of testing is needed for different chemicals. The final phase of the process—risk management—should include an evaluation of the costs, benefits, uncertainties, and technologies available for the various intervention strategies that could appropriately manage the identified risks. He noted that in the past too much time has been spent debating the technical content of the risk assessments while not enough time has been spent on the real purpose of risk assessment, which is making decisions that protect public health. He also noted that although epidemiology does not provide good dose-response data, it does provide information about the human health effects that result from exposures to complex, real world mixtures, including the products of interactions among different chemicals. In comparison, experimental toxicologists often use animal models to generate data about quantitative dose-response relationships and the full range of toxicological effects. He closed by envisioning the potential for a true alliance between epidemiologists and experimental toxicologists that could capitalize on the information strengths of each discipline.

The next presentation by Thomas McKone from the University of California, Berkeley focused on addressing current challenges in exposure assessment as part of a solutions-based approach to improving risk assessment. The speaker noted that current governmental regulations tend to limit the range of options for the risk management phase of risk assessment. His view was that the widest



possible array of options should be considered for public health and environmental problems due to chemicals, with an overall goal of improving community health. He stated that the exposure assessment component of risk assessment is complex due to temporal and spatial variability; diversity of sources, pathways, and exposure routes; and inter-individual variability. In addition, transport and transformation processes for chemicals, both in the environment and the body, can alter a compound and result in products that are often the compounds of interest. Biomarker measurements from human biomonitoring studies can provide useful data about compounds detected in samples, but these data often lack critical information about the exposure conditions related to the measured value. Another important aspect to consider is variability in individual susceptibilities due to endogenous factors, such as age, genetics, and pre-existing diseases, and exogenous factors, such as exposures to other

compounds. The speaker proposed that hypothesis-based research for exposure science be built on refutable hypotheses because the complete parameters of human exposure often cannot be known or identified in adequate detail. Through the use of exposure models and data, an optimal goal would be to test hypotheses regarding correlations between predicted exposures and those actually observed. Evaluation of case studies regarding exposures to indoor air pollutants is an approach that could be used to determine the value of melding models that incorporate both environmental and biomarker data.

The third speaker in this session, Mark Corrales from the EPA, addressed the challenges of incorporating genetic susceptibility into regulatory decision making. Exposure and susceptibility are two broad categories of variability and, although genetic susceptibility is a relatively recent consideration, its literature base has been growing rapidly. Susceptibility is only one aspect of how interactions between genes and environment (G X E) can affect risk. Genetic susceptibility and the potential impact of the environment is not a new idea, as demonstrated by its mention in several previous EPA documents (EPA 2009; 2006), but it has not yet been fully evaluated. Current risk assessment practices can oversimplify cancer risk and hazard index determinations and likely overestimate or underestimate these results for some individuals. Three different resources for data relevant to susceptibility are currently available. The first resource is data from gene expression arrays that can provide information on numerous chemicals but are not yet useful for quantifying susceptibility; they will be more useful when multiple animal strains and genotypes can be compared and when toxicity pathways are better understood. The comparative toxicogenomics database (CTD), a database of manually curated scientific articles with data on chemical-gene-disease relationships, currently contains results for approximately half of the compounds listed in the EPA's IRIS and is a valuable resource for understanding the inter-relationships between genes and chemicals. The second resource is pharmacokinetic and toxicokinetic data. Although pharmacokinetic data are only available for a limited number of compounds, they are useful for quantifying some components of variability and susceptibility; toxicokinetic data available for several enzymes involved in xenobiotic metabolism have demonstrated inter-individual variability. The third resource is data on human G X E epidemiology. This resource is currently limited to only a few chemicals, several of which are important to the EPA, but initial correlations indicate some links between epidemiological data on workplace exposures and genotype alterations. Since 2000, the Centers for Disease Control and Prevention (CDC) has managed the human gene epidemiology (HuGE) database, which contains manually curated G X E information from articles listed in PubMed. The diseases most often studied include cancers, cardiac disease, and obesity/diabetes, but agents in the environment are increasingly implicated in disease causation, such as G X E studies on asthma. Research on the interactions between specific genotypes and specific environmental factors is a newly emerging area, but it has the potential for important contributions to regulatory decision making.



## VI. Panel Discussion I

As noted earlier, several questions developed prior to the workshop served as starting points for the panel discussions, which included both the plenary speakers and invited speakers. The questions for the first panel discussion are included in the box below.

The first invited speaker, Michael Dourson from Toxicology Excellence for Risk Assessment, commented on the potential opportunities and drawbacks of making decisions based on what we know now by suggesting that we should address those problems that are most worrisome and assess the available information. If time and resources are available, he suggested a delay in decision making and support of research to reduce uncertainties. If decisions must be made, a path forward is to agree to revisit the issues as new data emerges. The recent NRC documents provide insights into the use of new genomics data for investigations on the mode of action of chemicals and support the concept of problem formulation as an approach to characterize risk problems. His position was that thresholds exist for all chemicals because, by definition, they reflect the starting point for adverse effects. He also noted that science contributes to the development of more balanced decisions and that informed restrictions based on more comprehensive risk assessments are needed.

The second speaker, Kathleen Plotzke from Dow Corning, summarized findings from a 2008 international workshop on persistent, bioaccumulative, and toxic (PBT) compounds and persistent organic pollutants (POPs) (Society of Environmental Toxicology and Chemistry [SETAC] 2009). The aim of that workshop was to foster advancement of a sound scientific foundation for identifying and evaluating PBT/POPs because the current regulations that define these compounds rely on rigid criteria based on science dating back to the late 1970s and early 1980s. A specific objective of that workshop was to reach consensus among the participants for developing guidance to evaluate compounds that may meet PBT/POPs criteria. The speaker commented that this SETAC workshop was a good example of a group of diverse stakeholders representing academia, industry, and government all working together, in this case, to better understand the state-of-the-science for PBT/POP compounds and formulate directions forward in an area of mutual interest.

The definition of thresholds was a focus of the comments from several participants following the invited speaker comments. Modes of action and how chemicals interact with biological receptors were other aspects mentioned as approaches that could be used to understand thresholds. One participant commented that it is debatable whether thresholds exist for all chemicals, and another participant noted that thresholds exist for both individuals and populations. Thresholds for individuals depend on numerous specific factors, including genetic differences and exposures to other chemicals. Given the variability of thresholds among individuals in a given population, the question of how to determine a

### Panel Discussion I Questions

- If the purpose of risk assessment is to make decisions that protect public health, how much science do we actually need to make effective decisions that are health-protective?
- What are the potential opportunities and drawbacks of making decisions based on what we know now?
- Do recommendations in recent NRC reports on toxicity testing and risk assessment form a workable basis for rethinking how risk assessment is done?

dose-response curve for a population was raised. Another discussion point was that health concerns should be considered using a broad-based approach rather than a chemical-by-chemical approach. It was noted that regulators have usually preferred a chemical-by-chemical approach for decision making but also want to know what options are available for controlling exposures. One participant suggested that although current risk assessments generally start with a specific chemical, risk assessments based on communities should also be considered. Another participant commented that community-based risk assessments have been an area of research interest for more than 10 years, and that the EPA recently hosted a workshop to decide how to move forward with this type of risk assessment.

## VII. Navigating Obstacles: New Approaches for Addressing Chemical Mixtures

The two speakers in this session provided provocative insights into the difficult problem of understanding the effects of exposures to complex mixtures of chemicals.

The first speaker, Andreas Kortenkamp from the University of London, introduced the concept of cumulative risk assessment, a risk assessment approach that groups together compounds that produce a common adverse effect. He used anti-androgens as a model to consider this approach. Anti-androgens, which include a number of phthalates, pesticides, and other man-made compounds, are



chemical compounds that can interfere with normal male hormone activity. For example, exposure to anti-androgens during the fetal life period can result in abnormal reproductive development. The speaker also reviewed results from several different studies about the effects produced by exposing rats to mixtures of anti-androgenic chemicals. The results indicated that the observed changes were greater than the effects produced by the most toxic chemical in the mixture alone; he also noted that these effects could be well-predicted by dose-addition methods. Based on these findings, he commented that chemical-by-chemical risk assessment approaches may underestimate the risks presented by combined exposures to multiple compounds, such as anti-androgens, even when the individual compounds used in experiments are at levels regarded as safe. These results introduced the important question of how best to conduct a cumulative risk assessment and how to group compounds that produce common adverse outcomes. He suggested either mechanistic or phenomenological criteria as a basis for the groupings, but he also commented that each approach presents problems. Whichever approach is selected, it must be plausible and

credible. The use of a hazard index, which is the sum of the ratios of the intake level to the acceptable intake level for different chemicals, may be a useful prioritization tool to identify knowledge gaps, direct epidemiological research, and focus regulatory action. He concluded by noting that the role of risk assessment is to protect human populations and that cumulative risk assessment could be a feasible approach to accomplish this goal.

The next presenter, Rogelio Tornero-Velez from the EPA, discussed the use of ecological models as an approach to understand multiple chemical exposures. He stated that a notable challenge for a risk assessment that includes multiple chemicals is considering the behavior of the chemicals in the mixture. Toxicologists and pharmacologists have previously developed approaches to address this challenge. However, little guidance is available to address the challenge of identifying which mixtures of chemicals in the environment are the most relevant and present the greatest concerns for toxicity and adverse effects. Because the possible combinations and permutations of chemicals in mixtures can be numerous, he suggested an approach that includes three generic types of mixtures: 1) defined - related by process; 2) similar - related by structure or mechanism; and 3) coincidental - occurring purely by chance (Sexton and Hattis 2007). He then discussed results from a community ecology model that examined 17 different species of finches on 19 West Indian islands that found that the presence or absence of different species on the different islands was not randomly distributed. Using a checkerboard analysis that indicated either the presence or absence of these species on the islands, the results showed that natural competition among the birds invoked “community assembly rules” and that two species predominated on each of the islands. As another example, he discussed a study that evaluated pesticide residues in floor wipe samples collected from child care centers and determined that not all combinations of pesticides were likely to be present. He concluded that the effect of structuring processes (non-randomness) limits the possible set of observed combinations. Similarly, chemical mixtures in the environment are subject, in part, to non-random processes, including economic factors, engineered formulations, and different degradation activities such that the observed set of combinations tends to be less diverse than the total number of possible combinations.

## VIII. Getting a Fix on Risk Assessment: Case Studies on How Science Might Help

This plenary session explored how currently available scientific information and information soon to be available can be used to advance risk assessment and what obstacles might prevent its use towards this objective.

The first speaker, Paul Price from the Dow Chemical Company, presented a case study that examined human dietary intake of chlorpyrifos, an insecticide used on multiple crops, as a model for estimating non-cancer health risks without the use of uncertainty factors. The study goal was to reduce the use of uncertainty factors employed in traditional non-cancer risk assessments by coupling physiologically-based pharmacokinetic (PBPK) models to human exposure models and to create one source-to-outcome model. Sources of uncertainty identified for this case study included model uncertainty, adequacy of the exposure data, ability to model dietary exposures, modeling age-related effects, and the ability to model the inhibition of acetylcholinesterase, which is an enzyme biomarker for chlorpyrifos activity. The approach for this study was to use multiple longitudinal dietary models, avoid unneeded complexity, and use



PBPK/pharmacodynamic models calibrated against animal and human data. The results indicated that this model was able to predict that the risk of adverse health effects from chlorpyrifos ingestion in humans was low without reliance on defaults inherent in animal-to-human or between individual (in this case adult-to-child) uncertainty factors. The study accomplished this by using data to model inter-individual variation in a population of 1,000 children and adults. Because uncertainty factors are intended to serve as substitutes for missing or uncertain data, their models avoided this requirement. The take-home lessons from this case study were that longitudinal modeling is essential, model predictions must match with biomonitoring data, human data are needed for calibrating the PBPK model, and predictions of risk are easier when exposure levels are well below the adverse effects levels.

In the second presentation, Robinan Gentry from ENVIRON International Corporation described a risk assessment case study that used innovative techniques to incorporate key events in the mode of action for a compound that acts through a receptor-mediated mechanism. The model compound used in this case study was phthalate di(2-ethylhexyl) phthalate (DEHP), a chemical that increases flexibility in



plastics including those used in numerous consumer products. This compound's anti-androgenic effects have been well-studied in animals, although fewer data are available for humans. Its modes of action have been hypothesized, and both PBPK models and biomonitoring data are available. The study evaluated a variety of endpoints from gavage, gavage/inhalation, and dietary studies to identify whether correlations could be identified between dosage and effects. Some patterns began to

emerge suggesting low-dose effects of DEHP in the gavage and inhalation studies; however, when they looked at dietary exposures—the route most relevant for humans—the low-dose effects were absent. Their conclusion was that statistical models are not always adequate for dose-response assessments and that integration of all available toxicological data is critical for understanding the biological processes impacted by chemical exposures. The speaker stated that consideration of those routes of exposure most relevant to humans should be given the highest priority in risk assessment. She concluded by commenting that these results likely apply to other compounds that act through receptor-mediated mechanisms.

## IX. Panel Discussion II

The questions developed for this second panel discussion are included in the box below.

The first invited speaker, Dennis Devlin from ExxonMobil, addressed the first question by stating that simplification of the risk assessment process should be secondary to the objective of advancing risk assessment for a wide range of chemicals and exposures. The advantages of simplifying risk assessment are reduced time, costs, and animal use, but a potential disadvantage is arriving at the wrong conclusions. He supported the objectives of the “The Silver Book” (NRC 2009) to increase early stage planning and scoping in risk assessment to meet the needs of decision makers. Regarding the second question, the speaker noted that because the potential costs of increased efficiency would likely be borne by society, costs must be considered relative to benefits. For the third question, he thought that the NRC reports provided useful recommendations, but that distinguishing adaptive responses from adverse responses and the proposed approach to eliminate thresholds needed further consideration. How to best incorporate emerging sciences into a new TSCA, and whether TSCA will have the flexibility to accommodate the ongoing developments in this new science, remain as current questions.

### Panel Discussion II Questions

- With the longer-term goal of modernizing chemical risk assessment, are there available methods and approaches that could be applied to simplify risk assessment? What are the pros and cons of a simplified approach?
- Will increased efficiency in risk assessment have unacceptable costs?
- Do recommendations in recent NRC reports on toxicity testing and risk assessment form a workable basis for rethinking how risk assessment is done?

Bob Sonawane from the EPA, the second invited speaker, agreed with the previous speaker’s comments on the first question. Regarding the second question of costs versus increased efficiency, he stated that risk assessment must first protect the public; although time and cost efficiencies could be achieved, losses or reductions in certain aspects of risk assessment based on cost, such as peer review, would be detrimental. He thought the NRC reports provided interesting approaches, but he did not yet clearly see how the emerging data could be used for dose-response analysis. He also mentioned the exposome, a concept proposed by Wild (2005) that considers all aspects of an individual’s exposures over a lifetime, but noted that more information about exposure is needed to better develop this concept.

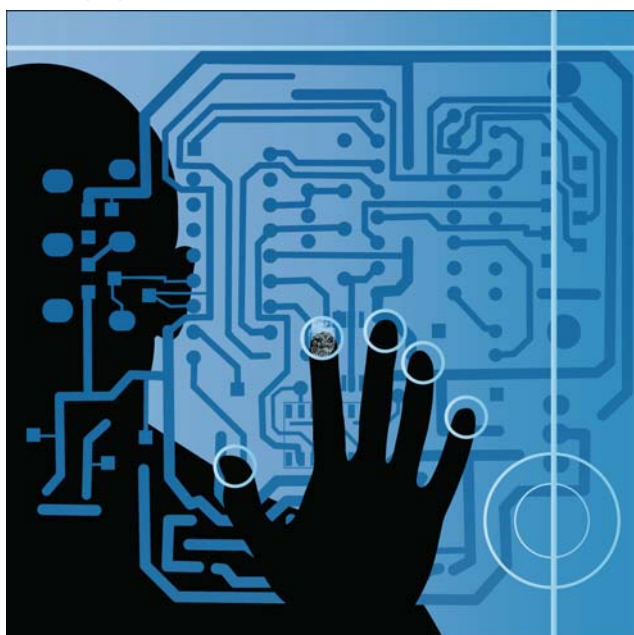
The third invited speaker, Ronald White from Johns Hopkins University, thought that simplifying risk assessment may be a good approach, but that the key objectives of risk assessment, such as setting priorities for research, determining a reference dose, and developing a basis for policy making, must first be defined. Although a simplified approach may save money, it should not raise more questions than it answers. The focus of the “The Silver Book” (NRC 2009) was to determine which questions needed answers. He agreed with the previous speakers that increasing efficiency could have unacceptable costs and noted that industry, society, and the ecosystem could all ultimately bear those costs. He thought that the 2007 NRC report (NRC 2007a) that discusses toxicity testing in the 21<sup>st</sup>



century will guide data generation in the future, but analyzing and integrating new test data into risk assessments will take time.

A variety of participant comments followed those of the invited speakers. One participant noted that modernizing risk assessment does not necessarily mean simplifying it because, in fact, it may become more complex. As an example of the importance of prior consideration to balance costs and benefits, a participant commented that the state of California had required flame retardants in clothing and fabrics to reduce fire hazards, but had not adequately anticipated the potential adverse health effects from exposures to these flame retardant chemicals in indoor environments. The advantages of the “The Silver Book” approach to upfront planning for risk assessment of chemicals were noted. Nanomaterials were also mentioned as an example where both the potential benefits and costs should be considered early in the risk assessment process.

Participants acknowledged the benefits of reducing animal use through the use of new technologies, but a path forward using these new technologies must be defined. One participant proposed his vision of a testing paradigm for a new chemical without the use of animals in which the first phase would determine the chemical’s proposed use and properties; the new chemical would then be incorporated into a population simulation model to determine which doses are safe. This would be followed by *in*



*vitro* studies using relevant doses, a review of the chemical’s metabolites, and determination of the lowest acceptable dose to avoid human health risks. The importance of moving to systems biology approaches and computational toxicity modeling to predict human toxicity was underscored by another participant’s comments. He noted that less than half of animal model studies accurately predicted adverse human outcomes. Both improved exposure assessment and computational toxicology models were noted as key components for modernizing risk assessment. The shift from the use of animal-based models to those using human tissues and cells will be critical for modernizing risk assessment. Finally, effective communication of the results emerging from these approaches to diverse audiences, from the public to decision makers, will be essential for acceptance.

## X. Emerging Science: Solutions or Barriers to Improving Risk Assessment?

This session provided insights into the possibility of incorporating data from new technologies, such as toxicogenomics, into risk assessment and of improving our understanding of correlations between the findings from *in vitro* testing and the effects from chemical exposures that occur in more complex biological systems.

The first speaker, Russell Thomas from the Hamner Institutes for Health Sciences, made the case for the importance of toxicogenomics in the advancement of risk assessment. He noted that genomics technologies, such as gene expression microarrays, have been used for more than a decade and that

multiple studies have demonstrated the reproducibility and sensitivity of current gene expression microarray technology. For dose-response studies, microarray analyses can provide quantitative information about the dose at which cellular processes are affected and the underlying biology of dose-dependent transitions. In his proposed approach for applying genomics to risk assessment, whole animals are exposed to different doses of the chemicals of concern and transcriptional changes are measured in the animals' target tissues using microarrays. A battery of statistical models is then used to plot the data for dose-response changes in transcription for selected cellular pathways or processes, such as cell proliferation. Points of departure (PODs) are then identified and used to estimate provisional reference doses (RfDs) or cancer slope factors for these compounds. He summarized the results from 90-day exposure studies using five chemicals and determined that reasonable correlations existed between the calculated transcriptional and traditional RfD values and cancer slope factor values, with some chemicals having better correlations than others. Overall, this approach looks promising; however, more work needs to be done to combine PODs for multiple steps that occur in the mode of action of a specific chemical. He is currently planning collaborations with the EPA's National Center for Environmental Assessment to evaluate the use of genomics for Tier II risk assessments, including studies to determine whether shorter-term exposure studies can be used to generate meaningful data.

The next presentation by Lesa Aylward from Summit Toxicology focused on dosimetry considerations to interpret the data from ToxCast™, a program at the EPA's National Center for Computational Toxicology designed to use HTS assays to identify the predictive toxicity signatures of chemicals and prioritize them for subsequent *in vivo* toxicity testing. The question was whether the chemical concentrations used in the *in vitro* HTS assays are relevant to those present in biological systems, such as the concentration data reported in human biomonitoring studies, including the CDC's National Health and Nutrition Examination Study (NHANES). To address this question, data were compiled from measurements of physiologically-relevant concentrations for five selected chemicals that included serum and plasma concentrations from animal and human biomonitoring studies and IRIS values, such as RfDs, lowest observable adverse effect levels (LOAELs), and no observable adverse effect levels (NOAELs) and then compared to concentrations used in the ToxCast assays. The results indicated that the range of concentrations for the five selected chemicals was wide, but they generally corresponded to physiologically-relevant concentrations; little evidence was found for extreme sensitivity or "sledge hammer" effects from the concentrations studied. One caveat for this approach is that it assumes that serum or plasma is similar to *in vivo* culture medium, which may or may not be the actual case. For example, most ToxCast assays are not specifically designed to generate biologically-relevant metabolites for chemicals. This is an important issue for *in vitro* testing because what produces a perturbation in a whole organism may be a compound metabolite rather than the parent compound. The EPA recognizes this issue and is developing tools to improve predictive toxicology. The speaker concluded her presentation by noting that effective chemical prioritization requires consideration of both toxicity and toxicokinetics, and that the chemical and physical properties of substances can be used to determine their toxicokinetic properties.



## XI. Panel Discussion III

The questions developed for the final panel discussion are included in the box below.

The first invited speaker, Stuart Cagen from Shell Oil Company, commented on the first question by stating that the new science will speak for itself. However, the EPA should provide leadership and oversight for discussions on the use of the new technologies to advance risk assessment. He noted several elements will be important to move the process forward. Trust in the science and in each other

### Panel Discussion III Questions

- What is required to enable the emerging (bio)technologies to invigorate and modernize risk assessment?
- Will increased efficiency in risk assessment have unacceptable costs?
- Do recommendations in recent NRC reports on toxicity testing and risk assessment form a workable basis for rethinking how risk assessment is done?

will be needed to insure that all stakeholders have the right intentions. He cautioned about a high-dose mentality and a focus on toxic effects observed at elevated doses because he considered this approach a potential barrier to generating information about lower doses. The temptation to use short cuts in the risk assessment process may exist, but validation is necessary.

Martin Stephens from the Humane Society of the United States, who was the second invited speaker, stated that he will measure the success of efforts to modernize risk assessment by the extent to which it replaces animal testing. He commented that he would like to see the vision and recommendations of the “The Silver Book” (NRC 2009) implemented quickly and faithfully. All models for evaluating toxicity have limitations, but the advancements of modern biology and 40 years of progress have not yet been effectively incorporated. The current paradigm must shift from one based on hazard to one based on safety and precaution for the use of chemicals.

ToxCast, Tox21, and other top-down approaches can help determine chemical signatures through a variety of assays, but it is important to be mindful of those fundamental pathways that have been conserved throughout evolution. Bottom-up approaches, in which pathways that can predict certain types of toxic effects are carefully assembled, can complement this process. This process involves monitoring key pathways and chemicals known to produce specific responses and then comparing the outcomes with assays; the Hamner Institute for Health Sciences is a pioneer of this approach. He noted that a substantial investment in resources will be required to implement the vision described in “The Silver Book” (NRC 2009), which had included establishment of a stand-alone institute. Because this institute is unlikely to be developed, a community of practice will be needed to discuss the issues that will advance risk assessment.

The third invited speaker, Ila Cote from the EPA, stated that working across the schisms in scientific opinions that exist in the risk assessment community will be needed to move forward. Her opinion was that a paradigm shift was needed, based on a systems biology view of disease and etiology, such as that used at the National Institutes of Health. Due to the large volume of data generated by the new biotechnology, one of the initial challenges will be sorting out meaningful changes from incidental changes. In addition, new approaches will be available for thinking about the most sensitive endpoints, individual thresholds versus population dose-response dynamics, and measuring the biomarkers of exposure and response. A number of issues will likely emerge from a new paradigm: how to define

adverse effects; which data are important; and, even when a molecular perturbation in the system that produces a disease is recognized, how will this information be used in risk management. Prototypes and case studies should be developed to work through these different issues. The education of risk managers and participation by a variety of stakeholders, including industry, government, and the public, will be an important component to the success of these efforts.

Participants provided a number of questions and comments following those of the invited speakers. The first questions focused on next steps and how to bring stakeholders to the table. One participant suggested the creation of a forum for interaction, or a community of practice. In addition, after further definition of the relevant issues, the EPA should organize a series of workshops to help define the topics for initial case studies. The process would likely involve three meetings and broad participation would be encouraged to discuss the strengths and weaknesses of the different approaches. One participant asked how this would be implemented within the scientific community, and another participant responded that he had been involved in this process in the lifecycle community. With help from the SETAC and the United Nations Environment Programme (UNEP), this community had formed small working groups of practitioners that were driven by a pre-existing work plan. The members of each working group generally provided their own funding. This process was effective and the groups were able to generate a lot of material and guidance. Another participant stated that the EPA is in the process of putting together draft prototypes that would serve as working documents for these types of working groups. The EPA is also reaching out to diverse groups of people to form working groups; they are scheduled to start within a year. On another point, one participant commented that the genomics and risk assessment communities do not know enough about each other. More communication is needed between risk assessors and the developers of new technologies to increase the understanding of how these technologies can be applied on a practical level.

## XII. Charting New Pathways Forward

The last plenary session focused on directions forward for modernizing risk assessment so that it can support sound decisions about chemicals that are in current use as well as new materials, such as nanomaterials. A theme of this session was that a reinvigorated risk assessment process should incorporate pragmatic and practical approaches that facilitate, not hinder, decision making.

The first presentation by Ronald White from Johns Hopkins University addressed current challenges and future opportunities in risk assessment related to the potential risks of nanomaterials. Nanomaterials have been defined as matter at dimensions between approximately 1 and 100 nanometers; examples of engineered nanomaterials include carbon nanotubes, fullerenes, and quantum dots. The increasing manufacture of engineered nanomaterials and their use in consumer products presents exposure concerns for workers, consumers, and the environment. The risk assessment challenges presented by nanomaterials include identifying critical hazard characteristics, such as chemical composition, particle size, structure, and coatings, as well as obtaining reliable exposure measurements. Exposure assessments are difficult due to limits of detection for current instruments; likewise, it is difficult to determine the relevant parameters to measure—e.g., size, mass, surface area, and/or number. Several



frameworks have been developed to address risk assessment and risk management of nanomaterials, such as lifecycle approaches that extend from the raw materials to the end of product life.

Comprehensive environmental assessment approaches have been developed to address concerns about the potential impacts of nanomaterials entering the environment, their fate and transport, and bioaccumulation. A current problem, however, is the lack of adequate data across all risk assessment steps. Validated *in vitro* assays are needed to evaluate free radical generation, cellular toxicity, cell activation, biopersistence, and other endpoints. HTS assays and QSAR can also be useful approaches as well as increased exposure assessments and the development of exposure biomarkers. Integration



of different frameworks and techniques should be considered to merge the classic risk assessment paradigms with life cycle analyses. Screening approaches could be utilized to prioritize hazard assessment and define the research needed for the emerging numbers and types of nanomaterials.

The final plenary presentation of the workshop by Bernard Goldstein of the University of Pittsburgh returned to the theme that the primary role of risk assessment is to protect public health. Prevention of adverse effects from exposures to chemicals in the environment should parallel a public health paradigm

that includes primary, secondary, and tertiary approaches. For primary approaches, the agent is never produced in large quantities or released into the environment if undesirable characteristics are identified during the initial testing and evaluation phases; secondary approaches identify methods that can avoid or minimize exposures to materials already in the environment; and tertiary approaches include medical treatments to manage adverse effects from prior exposures to materials. Exposure assessment is central to improving risk assessment; nanomaterials, as discussed previously, present an ideal opportunity to understand potential exposure concerns before significant exposures occur. He commented that methyl *tert*-butyl ether (MTBE), a fuel oxygenate additive, can serve as an example of the need for TSCA reform. This is because reports of human health symptoms following exposures while fueling vehicles as well as data about its adverse effects in animal models became available only after MTBE was widely introduced into motor vehicle fuels and, subsequently, the environment. The speaker also commented that individuals exposed to maximum concentrations do not accurately reflect the potential health concerns for the general public, but that individuals exposed to average levels can more accurately demonstrate these risks. The scientific and policy communities have a responsibility to insure that risk managers clearly understand the differences between these two exposure scenarios and their health implications. Although it will likely be a decade before results from the new technologies are incorporated into risk assessments, legislation is needed now to provide a means for these technologies to be effectively phased into risk assessment processes. Epidemiology has advanced in recent years and its ability to identify adverse health effects in population studies that were not previously identified in toxicological studies indicates a failure of the toxicological evaluation process. Improving exposure assessment is key to strengthening the power of epidemiological studies. The speaker concluded by commenting that uncertainty hampers the decision making ability of regulators because it complicates the formulation and defense of regulatory actions. More effort should be directed towards approaches and tools that can effectively manage the uncertainty aspects of risk assessment and fortify the decision making process.

### XIII. Workshop Summary

Several themes and recommendations emerged from the plenary and invited speaker presentations during the workshop, as well as from the thoughtful and insightful questions and comments from the workshop participants. They are summarized below:

- Risk assessment practices must be advanced so that they more efficiently and effectively protect public health. This effort will require scientific and policy input, as well as consensus among a variety of stakeholders, including academia, government, industry, and NGOs, as well as acceptance by the general public.
- Recent NRC reports provide numerous recommendations to significantly advance risk assessment; they include an approach that emphasizes planning and scoping in the initial assessment phase, decreased use of animals, use of new technologies, and consideration of the impacts of various risk management options and the associated costs. The NRC acknowledges that achieving these recommendations will take a substantial scientific effort over many years.
- The quality, quantity, and use of exposure assessment information must be increased to improve risk assessment; advancements in exposure models are needed to support these efforts.
- New approaches that address the effects of cumulative exposures to multiple substances and multiple stressors, particularly for susceptible populations such as children and the elderly, are needed to understand the health effects from everyday exposure conditions.
- Risk assessment practices that incorporate the use of new technologies, such as EPA's NexGen, and innovative approaches that consider exposures to chemical mixtures, including use of ecological models, are examples of ongoing efforts to modernize risk assessment.
- New technologies and bioinformatic sciences offer promising approaches to advance risk assessment and increase its efficiency; however, interpreting these new data and identifying approaches to effectively incorporate the data into risk assessment are current challenges.
- Increased transparency and communication in risk assessment and risk management processes must be part of a reinvigorated risk assessment that incorporates pragmatic and practical approaches and facilitates, rather than hinders, decision making.



## References

- American Chemistry Council. 2009. 10 Principles for Modernizing TSCA. Available at [www.americanchemistry.com/s\\_acc/sec\\_article\\_acc.asp?CID=2178&DID=9939](http://www.americanchemistry.com/s_acc/sec_article_acc.asp?CID=2178&DID=9939).
- National Research Council (NRC). 2009. Science and Decisions: Advancing Risk Assessment. The National Academies Press, Washington, DC.
- National Research Council. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. The National Academies Press, Washington, DC.
- National Research Council. 2007a. Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy. The National Academies Press, Washington, DC.
- National Research Council. 2007b. Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment. The National Academies Press, Washington, DC.
- National Research Council. 2007c. Models in Environmental Regulatory Decision Making. 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.
- Sexton K, Hattis D. 2007. Assessing cumulative health risks from exposure to environmental mixtures – three fundamental questions. *Environmental Health Perspectives* 115:825-832.
- Society of Environmental Toxicology and Chemistry. 2009. *Special Series: Science-Based Guidance and Framework for the Evaluation and Identification of PBTs and POPs*. Integrated Environmental Assessment and Management 5:535-711.
- U.S. Environmental Protection Agency (EPA). 2009. An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study (Final Report). U.S. Environmental Protection Agency, Washington, DC. EPA/600/R-09/028F.
- U.S. Environmental Protection Agency. 2006. *Summary of the NCEA Colloquium on Current Use and Future Needs of Genomics in Ecological and Human Health Risk Assessment*. National Center for Environmental Research, Washington, DC. Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA/600/R-04/039F
- U.S. Environmental Protection Agency. 2004. *An Examination of EPA Risk Assessment Principles and Practices*. Office of the Science Advisor, U.S. Environmental Protection Agency, Washington, DC. EPA/100/B-04/001
- 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.

## Participant Affiliations

American Association for the Advancement of Science  
American Chemistry Council  
Arch Chemicals, Inc.  
Army Public Health Command  
Bayer CropScience  
Bayer MaterialScience  
Cambridge Environmental Inc.  
Chemical & Engineering News  
Covanta Energy  
CropLife America  
Dainippon Sumitomo Pharma America, Inc.  
DakTox, LLC  
Dow Corning  
DuPont  
Eastman Chemical Company  
ENVIRON International Corporation  
Environmental Defense Fund  
European Food Safety Authority  
ExxonMobil Petroleum & Chemical  
George Washington University Law School  
Grocery Manufacturers Association  
Health and Environmental Sciences Institute  
Humane Society of the United States  
ICF International  
International Life Sciences Institute – Health and Environmental Sciences Institute  
Interfaculty Institute for Risk Assessment Sciences - Utrecht University  
University of Maryland – Joint Institute for Food Safety and Applied Nutrition  
Johns Hopkins University  
National Institutes of Health, National Library of Medicine  
Navy & Marine Corps Public Health Center  
Pesticide & Toxic Chemical News  
R.T. Vanderbilt Company, Inc  
Shell Oil Company  
Silicones Environmental, Health and Safety Council of North America  
Society of Chemical Manufacturers and Affiliates  
Summit Toxicology, LLP  
The Dow Chemical Company  
The Hamner Institutes for Health Sciences  
The LifeLine Group  
The Soap and Detergent Association  
Toxicology Excellence for Risk Assessment  
University of California, Berkeley  
University of London  
University of Pittsburgh  
U.S. Army Public Health Command  
U.S. Environmental Protection Agency  
U.S. Food and Drug Administration



## Final Workshop Program

**Tuesday, February 23, 2010**

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7:30 – 8:30 am **Registration and Continental Breakfast**

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8:30 am **Call to Order**

*Workshop Convener:* Tina Bahadori, American Chemistry Council

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8:35 am **Welcome**

Calvin Dooley, American Chemistry Council

Jan Mostowy, Bayer MaterialScience

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### Plenary Session I

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8:50 am **Setting a Course**

**From science to decisions: Moving beyond obstacles**

Paul Gilman, Covanta Energy Corporation

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9:15 am **Perspectives on Directions Forward**

**Human health risk assessment: EPA's current challenges and the future**

Peter Preuss, US Environmental Protection Agency (EPA)

**Confidential business information (CBI) and the credibility and transparency of risk assessment**

Richard Denison, Environmental Defense Fund

**Perspectives on directions forward: Challenges protecting children through science and opportunities for assessing and regulating chemicals with genomics and high throughput molecular screening techniques**

Richard Becker, American Chemistry Council

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10:30 – 11:00 am **Morning Break**

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Tuesday, February 23, 2010, Continued

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**Plenary Session II**

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11:00 am

**Advancing Risk Assessment: Considerations for Public Health Protection**

**Risk assessment for protection of public health: Random thoughts on some paths forward**

Joseph Rodricks, ENVIRON International Corporation

**Exposure assessment for a solutions-based risk assessment**

Thomas McKone, University of California, Berkeley

**Incorporating genetic susceptibility into regulatory decision making**

Mark Corrales, US EPA

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12:15 pm

**Panel Discussion**

*Moderator:* Brenda Barry, American Chemistry Council

*Panelists:* Michael Dourson, Toxicology Excellence for Risk Assessment; Kathy Plotzke, Dow Corning; and morning speakers

- If the purpose of risk assessment is to make decisions that protect public health, how much science do we actually need to make effective decisions that are health-protective?
  - What are the potential opportunities and drawbacks of making decisions based on what we know now?
  - Do recommendations in recent NRC reports on toxicity testing and risk assessment form a workable basis for rethinking how risk assessment is done?
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12:45 – 1:45 pm

**Lunch**

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**Plenary Session III**

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1:45 pm

**Navigating Obstacles: New Approaches for Addressing Chemical Mixtures**

**Cumulative risk assessment for antiandrogenic chemicals**

Andreas Kortenkamp, University of London

**Application of an ecological model to unravel multiple chemicals exposures**

Rogelio Tornero-Velez, US EPA

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2:45 – 3:15 pm

**Afternoon Break**

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**Tuesday, February 23, 2010, Continued**

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3:15 pm

**Getting a Fix on Risk Assessment: Case Studies on How Science Might Help**

**Characterizing risks of chemicals exhibiting extensive low dose clearance in the gut, liver, and blood: Dietary chlorpyrifos as a case example**

Paul Price, The Dow Chemical Company

**Challenges in the application of quantitative approaches in risk assessment: A case study with di(2-ethylhexyl) phthalate (DEHP)**

Robinan Gentry, ENVIRON International Corporation

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4:15 pm

**Panel Discussion**

*Moderator:* Annette Guiseppi-Elie, Dupont

*Panelists:* Dennis Devlin, ExxonMobil; Bob Sonawane, US EPA;

Ronald White, Johns Hopkins University; and afternoon speakers

- With the longer-term goal of modernizing chemical risk assessment, are there available methods and approaches that could be applied to simplify risk assessment? What are the pros and cons of a simplified approach?
  - Will increased efficiency in risk assessment have unacceptable costs?
  - Do recommendations in recent NRC reports on toxicity testing and risk assessment form a workable basis for rethinking how risk assessment is done?
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5:00 pm

**Evening Reception**

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**Wednesday, February 24, 2010**

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8:00 – 9:00 am

**Continental Breakfast**

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**Plenary Session IV**

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**Opening Remarks**

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9:00 am

**Emerging Science: Solutions or Barriers to Improving Risk Assessment?**

**Using transcriptomic data to define non-cancer and cancer points of departure: A five chemical case study**

Russell Thomas, The Hamner Institutes for Health Sciences

**Dosimetry considerations in interpretation of ToxCast™ data**

Lesa Aylward, Summit Toxicology, LLP

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**Wednesday, February 24, 2010, Continued**

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10:00 am

**Panel Discussion**

*Moderator:* Richard Phillips, ExxonMobil

*Panelists:* Stuart Cagen, Shell Oil Company; Ila Cote, US EPA;

Martin Stephens, Humane Society of the US; and speakers

- What is required to enable the emerging (bio)technologies to invigorate and modernize risk assessment?
- Do recommendations in recent NRC reports on toxicity testing and risk assessment form a workable basis for rethinking how risk assessment is done?

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10:30 am

**Charting New Pathways Forward**

**Assessing nanomaterial risks: Current challenges and future opportunities for risk assessment**

Ronald White, Johns Hopkins University

**Environmental risks and public health: Overcoming obstacles**

Bernard D. Goldstein, University of Pittsburgh

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12:00 pm

**Conclusion and Closing Remarks**

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