

ADVANCING EXPOSURE SCIENCE TO IMPROVE CHEMICAL SAFETY

WORKSHOP REPORT

The 2011 International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) workshop co-organized with Health Canada provided a rare, yet much needed opportunity for cross-disciplinary discussions about the exposure science needed to improve chemical safety assessments. For two days, nearly 100 international participants representing governments, academia, industry, and public advocacy groups attended platform presentations and actively engaged in panel discussions. This diverse audience brought together their expertise in toxicology, exposure science, environmental epidemiology, statistics, and regulatory policy to consider current issues and directions forward for exposure science. They reviewed, evaluated, and debated a variety of concepts, models, and measurement approaches that could efficiently and effectively advance understanding of potential health risks from exposures to chemicals. Their interactive discussions brought to light a number of areas that could benefit greatly from trans-disciplinary collaborations and innovations in exposure science. This report presents the highlights from this workshop and the ideas that emerged for the next generation of exposure science research.



No exposure, no risk – period.

~ International Society of Exposure Science, 2011

WHY ADVANCE EXPOSURE SCIENCE NOW?

The challenge for exposure science and the focus of this workshop were to address the current absence of innovative tools and approaches for assessing human exposures to chemicals. Fundamental and relevant assessment of the potential human health risks from chemicals depends on quality information about exposure as well as the hazards. However, to date, generation of information about chemical hazards has far outpaced that for exposure.

Meetings like this are important. They create an opportunity to bring together different scientific domains and sectors for a genuine exchange of ideas in an open and collegial manner.

~David Blakey, Health Canada

Since the 2007 publication of the National Research Council's Toxicity Testing in the 21st Century (National Research Council 2007), toxicology has been propelled into the 21st century through the development of new tools in molecular biology. These tools have been increasingly applied to assess chemical hazards and have rapidly accelerated methods for identifying changes in genes and in cellular metabolism following exposures to chemicals. High-throughput screening (HTS), stem cell biology, bioinformatics, and computational systems biology have all contributed to this advancement while dramatically decreasing the time and costs needed to generate the data. However,



this emerging volume of chemical hazard data must be grounded with relevant exposure data to appropriately assess health risks. Both data types are needed not only to address health concerns from the general public about product use, but also by regulators so that they can make informed decisions about risk based on an assessment of exposure and hazard.

By developing approaches that can quickly and efficiently provide the exposure data relevant for identifying potential health risks, exposure science can respond to its current challenge. The path forward requires a strategy that includes thoughtful, innovative, and tiered approaches to obtain the needed exposure information.

ADDRESSING BIOLOGICALLY-RELEVANT EXPOSURES

Getting at biologically-relevant exposures, that is, understanding whether or not the exposures that occur in daily life have the potential for adverse health impacts, was a workshop focus. Several speakers noted that traditional toxicity testing using animal models and high doses of chemicals has failed to closely resemble the “how” and the “how much” for actual human exposures. Biomonitoring studies and existing databases, such as the U.S. National Health and Nutrition Examination

We are on the cusp of an explosion of exposure data – the question is, how will we welcome the new reality that will come with the advancement of exposure science?

~Gina Solomon, National Resources Defense Council

Survey (NHANES) and the Canadian Health Measures Survey, were noted as valuable resources for data regarding the hundreds of compounds detected in the blood and urine samples collected from cross-sections of populations. The development of biomonitoring equivalents was also noted as a recent approach for linking the measured values to the human exposures that would be needed to produce those values. Yet, the context for understanding the potential health implications of the compounds detected by biomonitoring, often present at very low levels, as well as effects of chemical combinations are still missing.

How can models help fill current data gaps for exposure science? A goal for exposure models is to be predictive; yet, current exposure modeling is based on limited data that, in turn, limits its ability to be predictive. Confidence in these predictive models must be increased through better quality exposure data. Towards that end, exposure science research should be fit-for-purpose; that is, research questions must align with the appropriate investigative tools and the level of data detail needed to answer the study hypotheses. Data should be generated to calibrate and validate models, reflecting a conceptual understanding of the issues at hand. Ideally, the process should be iterative; data is fed into a model and data gaps are identified that can guide future data collection initiatives.

Quantitative information is essential for evaluating exposure models and biomonitoring data were identified as the best current source. To advance

our understanding of key processes related to exposure, it was also suggested that biomonitoring data be linked to source information from personal measurement devices. Several confounding factors that currently complicate meaningful interpretation of such data were also discussed, including variability among individuals and among populations and fluctuations in measured values due to the metabolism of chemicals following exposures.

Combining source-to-outcome modeling, a method that links exposure, physiologically-based pharmacokinetic (PBPK) modeling and biologically-based dose-response models and systems models, with the new molecular tools was another approach proposed for improving chemical risk assessment. This combined approach would focus on identifying early key events that can lead to adverse outcomes from chemical exposures rather than focusing on the later stage (apical) events usually identified by traditional toxicity testing.

A number of emerging technologies for measuring external exposures were discussed and included new miniaturized personal monitors, sensors for analyses of chemical exposures, and improved devices that can capture diet and physical activity data. Although these technologies are available now, they are applicable only for a limited number of chemicals and are not yet ready for wide use. Exposure science can advance through their continued development, validation of the monitors, sensors, and biomarkers, and implementation of integrative approaches.

Metabolic profiling, an emerging molecular technology that can detect the chemical footprints left by human cellular metabolism, was also described as an innovative approach that has promising applications for exposure science as a platform for information about individuals' internal metabolic processes. It also has the potential to identify novel biomarkers

of exposure and disease that can complement other molecular markers.

WINDOWS OF SUSCEPTIBILITY AND CHEMICAL EXPOSURES

What is the influence of early life exposures to chemical stressors on health outcomes later in life? Several presentations reviewed ongoing research to advance our understanding of the impacts of physiological and exposure conditions during relevant windows of susceptibility, particularly for infants and children. The studies discussed included the Canadian Maternal-Infant Research on Environmental Chemicals study as well as the NewGeneris project and Consortium to Perform Human Biomonitoring on a European Scale in Europe. The effects of exposures to chemicals during the perinatal and postnatal periods were a focus of interest due to the rapid growth and range of physiological changes that occur during these timeframes.

Laboratory research is also increasing our understanding of the impact of age on the responses of our systems to chemical exposures. Recent human studies indicate age-specific differences in the activity levels and effectiveness of



At the end of the day, we want to understand the potential health effects from chemical mixtures that we are exposed to in daily life.

~Elaine Cohen Hubal,
U.S. Environmental Protection Agency

enzyme systems designed to detoxify drugs and environmental toxicants. Such differences highlight the importance of developing PBPK models for predictive toxicology and risk assessment that account for different ages.

UNDERSTANDING CO-EXPOSURES TO CHEMICALS

In real life, we are not exposed to just one chemical at a time. Rather, humans are exposed to multiple chemicals and other stressors at any one point in time. Yet the majority of available data from studies in humans as well as animals is based on a single-chemical approach. Although evaluation of co-exposures is complicated, progress in this area is being made. Tiered approaches that apply increasingly refined hazard and exposure assessments to the different tiers have been developed as pragmatic approaches to assess risks from combination effects.

The World Health Organization/International Programme on Chemical Safety framework for risk assessment of combined exposures to multiple chemicals was discussed as an example of progress. This framework was designed to aid in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected. The maximum cumulative ratio (MCR), a tool developed to identify which populations and which groups of chemicals have the greatest need for an assessment of combined effects, was also reviewed. Another example presented used a tiered approach with a focus on evaluating consumers' exposures to the same chemical through multiple routes, such as inhalation and skin exposures.

What about statistical considerations when collecting and analyzing data for multiple chemicals, such as in biomonitoring studies? For example, how might measurement processes affect statistical inference for data on different biomarkers? What is the direction of correlations

between biomarkers and of correlations in the measurement processes when multiple analyses for numerous compounds are conducted using the same sample? Investigators were advised to consult with statisticians during their study design to better understand potential statistical pitfalls and to improve outcomes for their studies and predictive models prior to the start of data collection.

MAKING SENSE OF THE DATA

Innovative thinking will be essential to drive efforts to make sense of the data emerging from the new molecular technologies and apply them to identifying chemical hazards. Importantly, approaches that can link the concentrations of chemicals that produce effects *in vitro* to actual human doses of chemicals that result in similar concentrations in blood or tissues are needed to effectively interpret the data.

One such approach discussed incorporation of dosimetry with human exposure information to facilitate interpretation of results from high-throughput toxicity testing underway within the ToxCast™ program of the United States Environmental Protection Agency's (EPA) at its National Center for Computational Toxicology (NCCT). The results indicated where the amounts of chemicals measured in human samples overlapped with the levels of chemicals that produced in bioactivity in ToxCast's *in vitro* assays. Approaches such as these that include human exposure information can improve the basis for decision making in chemical prioritization activities.

Lessons can also be learned from the pharmaceutical industry. Drugs, which are chemical compounds designed to have specific biological effects, undergo rigorous pre-clinical high throughput and animal testing that is coupled with robust human clinical trials. The predictive approaches used in the drug development paradigm can help inform strategies for evaluating the effects of chemicals.

ADVANCING CHEMICAL SAFETY IN THE LIGHT OF EVOLVING SCIENCE

A global view of the key role of exposure science in advancing chemical regulation was provided by three presentations. A review of the Canada's Chemicals Management Plan outlined the importance of identifying and characterizing human exposures of potential concern as a fundamental step for providing the basis for policy decisions and regulatory actions.

The European perspective focused on the European Commission's Joint Research Centre and its research activities to improve *in vitro* approaches for understanding the effects of chemical exposures. This perspective emphasized an increased understanding of mode-of-action pathways for chemicals to determine the relevance of results from *in vitro* assays and HTS approaches as well as the critical need for good experimental design and quality control.

We need to develop efficient methods to understand exposures and prioritize chemicals for decision making; it will be a compromise between no data and sampling everything.

~Angelika Zidek, Health Canada

In the United States, the EPA's NCCT has initiated ExpoCast™, its program for conducting high-throughput exposure modeling as a parallel effort to its ToxCast™ program that uses HTS approaches to assess potential hazard. The EPA is also developing a systems level approach to identify adverse outcome pathways (AOPs) that are perturbed by environmental chemicals. AOPs can provide a framework for linking molecular level data to outcomes at the individual and populations levels.

SCIENCE – LOST IN TRANSLATION?

Effective communication of scientific information to non-technical audiences is challenging. All too often, key messages involving scientific issues, such as possible risks from chemical exposures during the workday and everyday life, are clouded or lost when the complex concepts and outcomes are presented to those who are not scientists or regulators.

Effective communication of new research findings about chemical exposures and the related regulatory and policy issues is critical so that stakeholders and the general public can understand their relevance to possible health concerns. An interesting point that was raised concerned the nodes of disconnect that can be created among regulators, industry, and consumers based on the different drivers that impact the thinking of each group. Am I protecting public health? Is the information provided sufficient? Am I and others safe? Does this product or technology improve my life? Each viewpoint is valid and each group should be mindful of other perspectives when addressing such questions.

PATHS FORWARD FOR EXPOSURE SCIENCE

The workshop became an incubator for exploratory discussions about future collaborative efforts among the participants. These discussions emerged from opportunities for the participants to hear and integrate perspectives from disciplines different from their own and to then consider new and alternative approaches for advancing exposure science.

An optimal outcome from these exploratory discussions would be activities to increase available exposure data, evaluate and improve models that can use the data to propagate exposure information from diverse

It is important to reassure the broader stakeholder community that the products that they are using are not causing problems. The science comes first, but we need to effectively communicate the outcomes of the science.

~Melanie Bausen, BASF SE

sources, and engage in ongoing human and toxicology studies to ground truth the findings. Such activities can and should be part of an overarching effort to advance exposure science using a holistic, system-based approach that incorporates multiple exposures, accounts for population vulnerabilities, and focuses on biologically-relevant tools and data.

Going forward, exposure science must be fit-for-purpose. High quality data obtained at high costs for all chemicals is neither realistic nor feasible if cost-benefit aspects and limited financial resources are truly considered. Resources must be directed at identifying those chemicals that present increased health risks based on the likelihood for exposure as well as their toxic properties. The cross-disciplinary interactions forged at this workshop contributed to the critical thinking and initiatives needed to advance the next generation of exposure science research and to improve chemical safety.

The International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) is a partnership that facilitates collaboration among the independently managed LRI research programs of the American Chemistry Council (ACC), the European Chemical Industry Council (Cefic), and the Japan Chemical Industry Association (JCIA). More information about ICCA-LRI and its supporting organizations can be found at www.icca-chem.org.