

What Will Work?

Application of New Approaches for Chemical Safety Assessment

To actualize the promise of new technologies to rapidly and cost-effectively provide data for assessing the safety of chemicals, scientific confidence needs to be built to underpin reliance on these methods for decision making for regulatory and product stewardship decision making. Under the theme *What Will Work?*, the 2015 International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) workshop examined current and future advancements in technologies for generating bioactivity, hazard and exposure data and predictions and discussed challenges and opportunities for potential uses in priority setting, screening and chemical safety determinations. Organized in collaboration with the U.S. Environmental Protection Agency, the workshop was held in New Orleans, Louisiana, USA on June 16th and 17th 2015.

Workshop Highlights The workshop opened with three plenary presentations providing overviews of North America, Europe, and Japan, focusing on advances in hazard and exposure assessment for chemical safety. North American approaches focus on incorporation of technological advancements and data from both hazard and exposure assessments for risk-based approaches, whereas in Europe, there is an emphasis on increased use of *in vitro* testing and read-across methods for hazard-based approaches for classification and labelling. In Japan, a risk-based approach to chemical safety is favored, with both exposure information and quantitative structure activity relationship (QSAR) data considered important components for chemical safety determinations.

The first session, *What Is Working?* reviewed case studies of current innovative approaches in chemical safety assessment. The U.S. Environmental Protection Agency's Endocrine Disruptor Screening Program was described as the first effort by the agency to use high-throughput screening results for regulatory decisions on chemicals. The program is showing promise, particularly for chemical prioritization, but ongoing challenges include distinguishing specific responses from cytotoxicity and physicochemical responses and establishing predictive model performance. Current application of read-across and QSAR approaches for untested chemicals and chemicals with limited data sets were also discussed. Challenges include difficulties in developing consistent opinions by experts in academia, industry and regulatory agencies for read-across assessments for complex toxicities, especially for substances with limited datasets.

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In the session *What Will Work?*, the adverse outcome pathway (AOP) was introduced as a conceptual framework for linking initial molecular interactions, through a series of key events consisting of cellular changes followed by tissue responses, to an adverse outcome in an individual or population. While systems biology approaches and dosimetry modeling will be needed to connect molecular and cellular events following chemical exposures and inform AOPs, the goal is for AOPs to be used, drawing from a variety of datasets, for regulatory applications such as category formation, read-across, hazard evaluation and risk assessment. Advances in toxicogenomics, innovative approaches to group chemical structural data, and initiatives that combine *in vitro/in silico* systems for predictive toxicology are proving to be valuable data sources. Regarding the exposure information critical for risk-based decision making, significant progress has recently been made in predictive exposure modeling for estimating human and ecological exposures. Research to improve exposure predictions is accelerating, and information from different modeling approaches can be combined to both verify and add power to the predicted exposure estimates. The challenges of integrating pathway and exposure information were reviewed as part of efforts towards risk-based evaluations. Comparison of data from fruit and vegetable extracts with data from chemicals obtained using the same assay system provided a real world context for the data and an impetus for thoughtful future interpretation of high-throughput *in vitro* data.

The *Bridging the Gap* session explored how to address the challenges faced when incorporating emerging approaches into chemical safety evaluation processes. AOPs and improved QSAR models were presented as examples of ongoing approaches that could provide bridges between existing and emerging data. As an added perspective from the pharmaceutical industry, quantitative systems pharmacology was discussed as an approach that uses networks of information to predict or characterize mechanisms for adverse outcomes in drug testing that may be applicable to chemical testing. To close the session, effective communication to the general public regarding scientific confidence in chemical evaluations based on these advanced approaches was highlighted as an important objective.

Summary This workshop highlighted both the promises offered and the challenges faced by the new technologies for advancing chemical safety assessment. These new technologies are already demonstrating success for chemical screening and prioritization and are catalyzing the transition from traditional animal toxicity testing. While significant advancements have been realized in characterizing the bioactivity of chemicals and exposure science, further research is critical to improve methods, extend the domains of applicability and to establish the requisite degree of scientific confidence needed so that all stakeholders can have trust in the use of these approaches for chemical safety assessment applications in regulatory decision making.

The ICCA-LRI is a global research program under the auspices of the ICCA and includes LRI programs supported by the [American Chemistry Council](#), the [European Chemical Industry Council](#) and the [Japan Chemical Industry Association](#). A hallmark of the annual ICCA-LRI workshops is to bring together a diverse range of stakeholders, including governmental and regulatory agencies, academia, and industry, and promote dialogue and advance thinking on issues of mutual interest in chemical safety.