Accelerating the Pace of Chemical Risk Assessment Workshop: Advancing Progress in the Use of New Alternative Methods for Regulatory Support

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Abstract

The tides of acceptance of new alternative methods (NAMs) are changing. Numerous scientific papers have been published recently that explore the boundaries of data applicability and propose approaches that bridge new and conventional methods. The modernization of the Toxic Substances Control Act, the implementation of REACH, the next phase of the Canadian Chemicals Management Plan, and many international chemical management policies and laws have escalated the demand for sharing of data and knowledge across the regulatory landscape. This surge in scientific interest and regulatory demand provided the momentum to examine how NAMs might transform regulatory evaluation of chemicals and pragmatically evaluate barriers to acceptance. These barriers include potential limitations of existing technologies, differing regulatory needs for decision making, and lack of understanding in applying NAMs. In order to better understand what is needed for the acceptance of the use of NAMs for chemical risk assessment, recent workshops were convened comprising key international regulatory agencies to discuss progress in applying the new tools to prioritization, screening, and application to quantitative risk assessment (RAs) of differing levels of complexity. Most progress has been made in screening and prioritization, but ultimately to modernize quantitative risk assessment, there is a need to demonstrate how the data and tools can be incorporated into future RAs. Scientific and regulatory needs for the quantitative application of NAMs to RAs were identified, and example case studies were undertaken as intergovernmental collaborations to address these needs. Case study topics include use of NAMs for exposure evaluation, assessing data poor chemicals, or specific chemical classes, including per- and poly-fluorinated substances. Results of these case studies will be presented and the role of the NAM to address the chemical management or risk assessment challenge will be discussed. These efforts are an important step in increasing the confidence in use and acceptance of NAMs in regulatory chemical risk assessment.

Goal and Participants

- To bring together international government regulators and researchers to discuss progress and barriers in applying new approach methodologies (NAMs)[1] to prioritization, screening, and quantitative risk assessment of differing levels of complexity.
- Participants from ECHA, EFSA, JRC, INERIS, RIVM, EPA, NTP, NICNAS, OECD, Health Canada, Environment and Climate Change Canada, ASTAR, SAHTECH, Seoul National University (Korea), NITE (Japan)

[1]New approach methodologies (NAMs) are defined broadly here as including in silico approaches, in chemico and in vitro assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard.

Ongoing Case Studies

Case Study Topic	Description	Current Status
Application to Risk Evaluation		
Bioactivity as a conservative estimate of no- and low effect levels in traditional animal studies *SOT abstract 2554 –K. Paul Friedman and R Thomas; Tues March 13*	• Retrospective comparison of points of departure (PODs) from NAMs (e.g., high-throughput in vitro bioactivity data) to PODs from traditional animal toxicity studies for 380 chemicals • Demonstrate the applicability of the bioactivity-to-exposure ratio (BER) as a means for risk-based prioritization	• PODs from NAMs appear conservative approx. 90% of the time • Evaluating uncertainties and areas for improvement in the use of PODs from NAMs for screening level risk assessment • BERs derived for all 380 chemicals • Manuscript submission in 2018
Quantitative and qualitative comparison of NAMs and traditional animal toxicity testing for data poor chemicals	• Prospective case study to evaluate the qualitative and quantitative concordance of NAMs and traditional animal toxicity testing • Will build off of the retrospective case study described above • Use for hazard characterization and quantitative analysis if possible	• Substances selected for Phase 1 testing under review • Anticipated testing start date March 2018
Application to Chemical Categorization		
Systematic review of literature on per- and polyfluoralkyl substances (PFAS) family of chemicals followed by NAMs analysis of various toxicities	• Using multiple approaches for determining the scope of the available data • Tiered targeted high-throughput toxicity and toxicokinetic testing with a focus on toxicological endpoints of interest .	• Comprehensive review of literature for selected PFAS. • Identifying PFAS to be used in Tier 1 toxicity testing to support read across efforts, with a focus on hepatotoxicity, developmental toxicity, and immunotoxicity.
Understanding chemical categorizations	• Develop NAM profiles based on available data (e.g., highthroughput in vitro assay data) for existing chemical categories • Consider grouping chemicals on the basis of NAM profile (e.g., chemotypes and structure) • Use of NAM data to develop categories	• Focusing in on 3-5 chemical categories for use in defining endpoints of interest. • When endpoints are determined, will acquire NAMs data related to appropriate apical endpoints.
Application to Exposure Evaluation		
Triaging chemical exposure data needs and tools for next-generation risk assessment	• Including NAMs for exposure, including computational exposure science and *in silico* approaches. • Expanding use of high-throughput exposure methods, like non-targeted analysis and quantitative structure-activity relationship (QSAR) models.	• Formalization and publication of data landscape evaluation for manufactured chemicals. • Beginning evaluation of use of QSAR models for chemical functional use and comparison of EPA pathway specific HT exposure models to traditional assessments.
Use of innovative modeling and GIS approaches by various agencies for assessing lead exposures	• Using Pb as a case study, highlights issues of screening level vs higher tier exposure assessment methods. • Example of use of new multimedia exposure-dose modeling to inform risk assessments and health-based decision-making.	• Summary of various modeling/GIS approaches; comparison of the various multimedia exposure-dose Pb modeling approaches, input data used, and results for Pb which could inform modeling analyses for other chemicals of international interest (e.g., PFAS).

Key Questions

- **What are the current barriers to acceptance for successful use of NAMs in regulatory decision-making?**
  - Benchmarking NAMs against laboratory animal studies
  - Potential limitations of existing technologies and their coverage of biology
  - Lack of understanding and confidence in applying NAMs
  - Differing regulatory needs for decision making, with some requiring specific testing requirements
- **What are near-term efforts that can improve use of NAM data?**
  - Analysis of the uncertainties related to NAMs
  - Addressing the limitations of NAMs (e.g., metabolic competence)
  - Explore new ways of describing hazard in ways that NAMs are designed to address (e.g., bioactivity in a certain pathway) and map to risk or safety evaluation
- **What is needed to lead to acceptance of NAMs by regulators and the public?**
  - Increased training and education
  - Communication on the use of NAMs
  - Broader collaboration and more demonstration case studies

Next Steps

Exploring and addressing gaps in the understanding and acceptance of NAMs for regulatory decisions making through:

- Continuation and completion of collaborative case studies.
- Development of new case studies to potentially address specific regulatory decisions:
  - Existing data gaps in use of NAMs for regulatory decision-making
  - Advancing acceptance of NAMs for use in regulatory decision-making
  - Increasing understanding of NAMs for use in exposure analysis
- Incorporate relevant case study activities into OECD working groups for broader international engagement
- Continued engagement with regulators; advocating for data and knowledge sharing.

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