APCRA

ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Update on APCRA Activities and Progress

OECD WPHA meeting
June 24-25, 2021

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Reminder on the Vision for APCRA

APCRA is an international governmental collaboration that brings together governmental entities engaged in development of new hazard, exposure, and risk assessment methods and approaches for their chemical evaluation activities.

- To discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.
- To discuss opportunities to increase collaboration in order to accelerate the pace of chemical risk assessment.

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Goals of APCRA

- Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context.
- Increased understanding of realistic benchmarks for performance of NAMs in different regulatory contexts.
- Determine mechanisms to enhance data sharing capabilities.
- Increase engagement and commitment to development and sharing of case studies of mutual interest.
- Increased cross-Agency collaboration to strategically address barriers and limitations of use of NAMs in a regulatory context.

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Requirements for APCRA Case Studies

- Promote collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in clear regulatory context.
- Include international, cross-agency representation on a topic of mutual interest.
- Demonstrate consistent progress towards the scientific and translational goals.
- Communicate results through presentations at professional meetings and publications.

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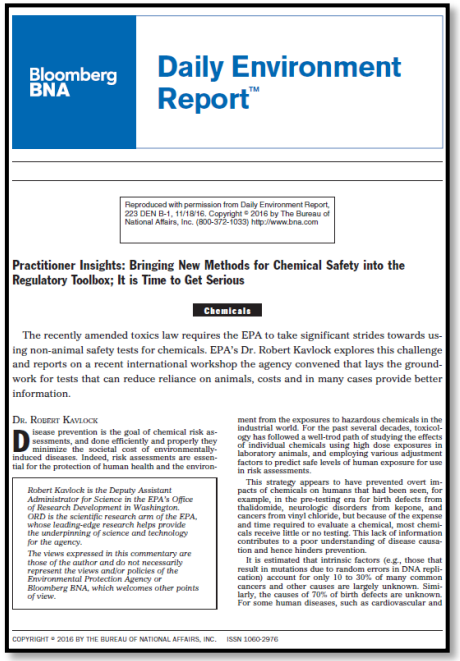
Participants




- **United States:** EPA, California EPA, NTP, CPSC, FDA, NIH
- **Canada:** Health Canada, Environment Climate Change Canada
- **Europe:** ECHA, EFSA, JRC, INERIS, RIVM
- **Asia:** Korea – Ministry of the Environment, Japan – Ministry of the Environment & Ministry of Health, Welfare and Labour, Singapore – A*STAR, Taiwan – SAHTECH
- **Australia:** AICIS
- **OECD**

Themes and Outcomes of Previous Workshops

APCRA-1



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Practitioner Insights: Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious

Chemicals

The recently amended toxics law requires the EPA to take significant strides towards using non-animal safety tests for chemicals. EPA's Dr. Robert Kavlock explores this challenge and reports on a recent international workshop the agency convened that lays the groundwork for tests that can reduce reliance on animals, costs and in many cases provide better information.

DR. ROBERT KAVLOCK

Disease prevention is the goal of chemical risk assessments, and done efficiently and properly they minimize the societal cost of environmentally-induced diseases. Indeed, risk assessments are essential for the protection of human health and the environment from the exposures to hazardous chemicals in the industrial world. For the past several decades, toxicology has followed a well-trod path of studying the effects of individual chemicals using high dose exposures in laboratory animals, and employing various adjustment factors to predict safe levels of human exposure for use in risk assessments.

Robert Kavlock is the Deputy Assistant Administrator for Science in the EPA's Office of Research Development in Washington. ORD is the scientific research arm of the EPA, whose leading-edge research helps provide the underpinning of science and technology for the agency.

The views expressed in this commentary are those of the author and do not necessarily represent the views and/or policies of the Environmental Protection Agency or Bloomberg BNA, which welcomes other points of view.

This strategy appears to have prevented overt impacts of chemicals on humans that had been seen, for example, in the pre-testing era for birth defects from thalidomide, neurologic disorders from kepone, and cancers from vinyl chloride, but because of the expense and time required to evaluate a chemical, most chemicals receive little or no testing. This lack of information contributes to a poor understanding of disease causation and hence hinders prevention.

It is estimated that intrinsic factors (e.g., those that result in mutations due to random errors in DNA replication) account for only 10 to 30% of many common cancers and other causes are largely unknown. Similarly, the causes of 70% of birth defects are unknown. For some human diseases, such as cardiovascular and

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- Common understanding of current state of the science applications of NAMs, including the regulatory context
- Commitment to development and sharing of case studies of mutual interest

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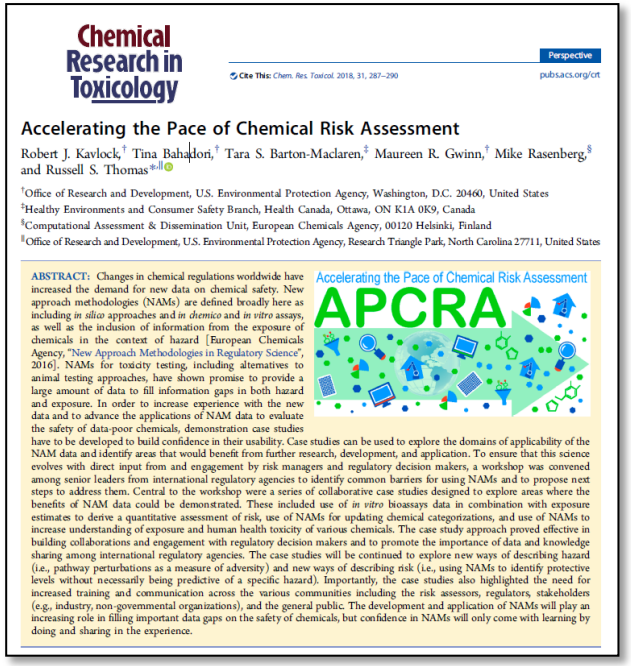

Chemical Research in Toxicology

Perspective

Cite This: *Chem. Res. Toxicol.* 2018, 31, 287−290

pubs.acs.org/crt

Accelerating the Pace of Chemical Risk Assessment

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ABSTRACT: Changes in chemical regulations worldwide have increased the demand for new data on chemical safety. New approach methodologies (NAMs) are defined broadly here as including *in silico* approaches and *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard [European Chemicals Agency, "New Approach Methodologies in Regulatory Science", 2016]. NAMs for toxicity testing, including alternatives to animal testing approaches, have shown promise to provide a large amount of data to fill information gaps in both hazard and exposure. In order to increase experience with the new data and to advance the applications of NAM data to evaluate the safety of data-poor chemicals, demonstration case studies have to be developed to build confidence in their usability. Case studies can be used to explore the domains of applicability of the NAM data and identify areas that would benefit from further research, development, and application. To ensure that this science evolves with direct input from and engagement by risk managers and regulatory decision makers, a workshop was convened among senior leaders from international regulatory agencies to identify common barriers for using NAMs and to propose next steps to address them. Central to the workshop were a series of collaborative case studies designed to explore areas where the benefits of NAM data could be demonstrated. These included use of *in vitro* bioassays data in combination with exposure estimates to derive a quantitative assessment of risk, use of NAMs for updating chemical categorizations, and use of NAMs to increase understanding of exposure and human health toxicity of various chemicals. The case study approach proved effective in building collaborations and engagement with regulatory decision makers and to promote the importance of data and knowledge sharing among international regulatory agencies. The case studies will be continued to explore new ways of describing hazard (i.e., pathway perturbations as a measure of adversity) and new ways of describing risk (i.e., using NAMs to identify protective levels without necessarily being predictive of a specific hazard). Importantly, the case studies also highlighted the need for increased training and communication across the various communities including the risk assessors, regulators, stakeholders (e.g., industry, non-governmental organizations), and the general public. The development and application of NAMs will play an increasing role in filling important data gaps on the safety of chemicals, but confidence in NAMs will only come with learning by doing and sharing in the experience.

- Identify and develop strategies to address critical data gaps
- Understanding requirements for acceptance of NAMs by regulators and the public
- Add exposure NAMs to case studies

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INSIGHT: New Approaches to Chemical Assessment – a Progress Report

TARA BARTON-MACLAREN, HEALTH CANADA; MAUREEN GWINN, ENVIRONMENTAL PROTECTION AGENCY; DR. RUSSELL THOMAS, ENVIRONMENTAL PROTECTION AGENCY; ROBERT KAVLOCK, KAVLOCK CONSULTING LLC; MICHAEL RASENBERG, EUROPEAN CHEMICALS AGENCY

New Approach Methodologies (NAMs) for chemical hazard, exposure, and risk assessment are emerging tools that have the potential to increase the throughput of chemicals testing through analytical assays and bring robustness and mechanistic knowledge to chemical assessment. Recent advances in the development and application of NAMs in various research and regulatory contexts has set the stage for a transformation in toxicology that the U.S. National Academy of Science envisioned more than a decade ago.

Fast and Protective But before they can be formally adopted for use in risk assessment, we need to ensure that New Approach Methodologies will provide appropriate protection levels for human health and the environment.

Adopting these new approaches in chemicals regulation requires at least three essential elements: a solid scientific foundation demonstrating their robustness, validity, and general availability; public confidence in their ability to ensure protection of human health and the environment; and policy adoptions by national regulatory bodies that will enable chemical industry compliance. While there has been significant movement by regulatory agencies in this later regard (e.g., European Chemicals Agency, U.S. EPA, and Health Canada), coordination on the international level will be critical to ensuring barriers to adoption will be kept to a minimum.

One important effort to identify and overcome barriers to regulatory acceptance of NAMs is the Accelerating the Pace of Chemical Risk Assessment (APCRA) project, which began with a meeting of international regulatory agencies that the U.S. EPA hosted in 2016, with a follow up in Helsinki in 2017 that the European Chemicals Agency (ECHA) hosted. Building on the success of those two meetings, Health Canada hosted the third meeting in October 2018 in Ottawa. The main objectives of the Ottawa meeting were to review progress on a number of case studies that were specifically developed during the previous two meetings to build confidence in NAM application, expand the portfolio of case studies to include ecotoxicological examples, and discuss future directions of APCRA.

While attendance to the APCRA meetings has been limited to scientists from national regulatory agencies (many participants strongly feel this is one of the unique and valuable attributes of APCRA as it enables frank and open discussions), the Ottawa meeting included an open public session in which 120 attendees from academia, international and state governments, industry, and nongovernmental organizations participated via remote access. This session served as a key opportunity to share progress and findings to date with public stakeholders. Given the positive response to this session, the organizers are discussing further public outreach for the future.

Down to Cases In addition to a general overview of the Accelerating the Pace of Chemical Risk Assessment effort, the public session also included a presentation of three of the most advanced case studies.

The first case study, led by the U.S. EPA, is a retrospective comparison of whether in vitro bioactivity, as measured in ToxCast, can be used to derive a conservative point of departure (POD) for prioritizing and screening level risk assessments.

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- Establish confidence in use of NAMs in terms of comparisons to traditional methods and integrating divergent data streams
- Add ecological NAMs to case studies
- Increase outreach efforts, both internally and publicly
- Strategic direction for APCRA

Themes and Outcomes of Previous Workshops

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- Progress in integrating NAMs across regulatory jurisdictions
- Grounding NAMs using systematic review tools

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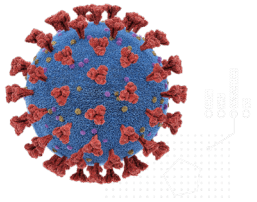

- Continued shared learning on state of the science applications of NAMs through case studies
- Common understanding on what is critical to achieve, important to achieve, and critical to avoid

APCRA-6

Coming Fall 2021

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Completed APCRA Case Studies

Case Study	Lead organization	Outcomes
Retrospective Case Study Examining the Utility of In Vitro Bioactivity as a Conservative Point of Departure	US EPA Health Canada ECHA	Toxicol Sci. 2019 doi: 10.1093/toxsci/kfz201
Use of transcription profiles and primary human liver cells grown as spheroids to address potency and additivity of perfluorinated alkylated substances: Applications for read-across and additivity in risk assessment of emerging PFAS	Health Canada A*STAR	October 2020 – preprint https://www.biorxiv.org/content/10.1101/2020.10.20.347328v1 March 2021 – PUBLISHED Toxicol Sci, 181(2), June 2021, pp 199–214
Evaluation of Quantitative Structure Use Relationship (QSUR) Models with Industry-Reported Data –US EPA	US EPA Health Canada	Publication pending
Linking Exposure to Toxicology Using Lead as Case Study	US EPA	Publication pending
Further Exploration of High-Throughput and Traditional Exposure Estimates to Advance NAM and Prioritization Tools for Exposure	Health Canada	Publication pending
Evaluation of the zebrafish (Brachydanio rerio) model as an in vivo NAM that serves as an alternative to rodent assays for validating in vitro assays in the assessment of chemicals for general toxicity and endocrine disruption	Health Canada	Toxics. 2020 doi: 10.3390/toxics8040126

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Ongoing APCRA Case Studies

Case Study	Lead organization
Prospective Case Study to assess chemicals, using and developing New Approach Methodologies (NAM)	ECHA
Investigating the applicability of bioactivity data to inform quantitative hazard assessments for ecological species using bioactivity-to-exposure ratios (eco-BER)	Environment Climate Change Canada
Transcriptomics-based points of departure for ecotoxicology	US EPA
In vitro assessment of digestibility and gastrointestinal absorption of nanofibers	European Food Safety Authority
A NAM-Based Integrated Approach for Screening Potential Genotoxic Chemicals	Health Canada
EDC-NAM Categorization	INERIS
Revisiting and updating chemical categorizations with new approach methods (NAMs)	US EPA
High Throughput Toxicokinetics for In Vitro-In Vivo Extrapolation	US EPA
Substantiating Chemical Categories with Omics-derived Mechanistic Evidence (SuCCess)	ECHA

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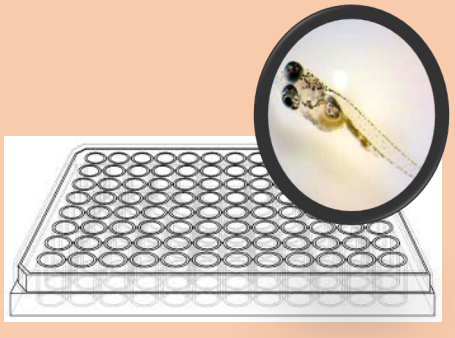
Transcriptomics-Based PODs for Ecotoxicology Case Study

Preliminary Results

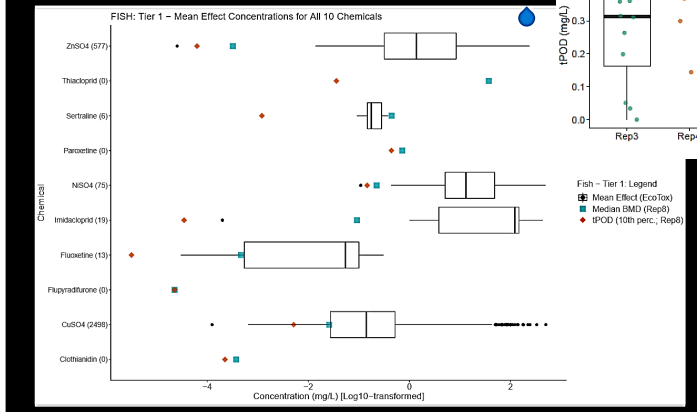
Objectives:

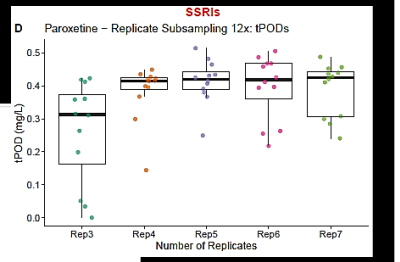
- Generate tPODs for ≈ 20 chemicals
- Compare tPODs with traditional acute and chronic toxicity data (ECOTOX)
- Compare tPODs with PODs derived from ToxCast



24 h exposure
96 well format
5-6 dpf fathead minnow

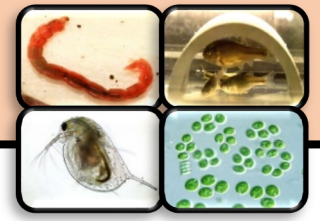
- tPODs generated for 10 chemicals
- tPOD < effect concentrations coded in ECOTOX
- In-silico subsampling used to:
  - Optimize exposure design
  - Develop assay acceptance criteria and tPOD uncertainty estimates





On-going:

- Fathead minnow exposures completed for 11 more chemicals
- Awaiting sequencing results
- Incorporated analytical verification of conc.
- Conducting HTP exposures with daphnia, chironomids, algae for 21 compounds



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Prospective Case Study for Assessing Chemicals Using NAMs

Objectives:

- Assess chemicals with limited/unclear toxicological data, using both NAM type of data and classical toxicological studies
- Inform the further development needs for NAM:
  - Screening, prioritization and first tier assessments;
  - Conclusive hazard characterization/ assessment and risk management;
- Build experience and confidence in application of NAMs
- Assess chemicals in an international context

Current Status:

- Methodology for data integration and processing agreed
- *In vitro* results (Tier 1) have been generated and provided to EPA for analysis, normalization and integration
- The current regulatory status of the APCRA substances has been checked
- Processing of Tier 1 data to identify candidates for further testing is foreseen to be finalized by end of June
- Substance selection for further testing (5d multi-omics rodent assay or other systemic tox study) will be done over the summer
- Anticipate start of *in vivo* testing in the fall

200 substances – 8 toxicodynamic assay platforms including broad and targeted NAMs
Use of toxicokinetic NAMs for dose prediction – Use of models and data for hazard flags

EPA United States Environmental Protection Agency
Health Canada www.hc-sc.gc.ca
A*STAR SINGAPORE Agency for Science, Technology and Research
ECHA EUROPEAN CHEMICALS AGENCY
rivm National Institute for Public Health and the Environment
NTP National Toxicology Program U.S. Department of Health and Human Services
EURL ECVAM European Union Reference Laboratory for Alternatives to Animal Testing
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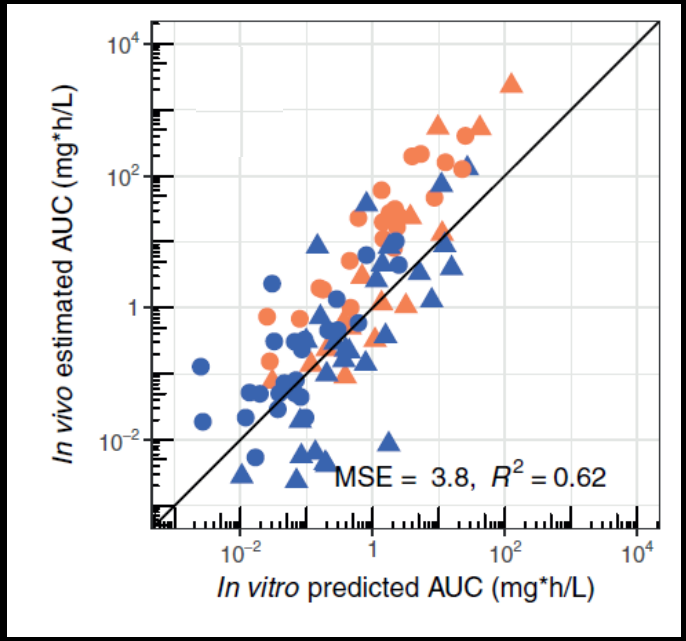
High Throughput Toxicokinetics for *In Vitro*-to-*In Vivo* Extrapolation Case Study

Objectives:

- Develop a decision tree for the development of high-throughput toxicokinetic models parameterized by *in vitro* data and *in silico* models
- Increase model complexity and experimental data depending on:
  - Decision context
  - Chemical context
- Evaluate model uncertainty across decisions and chemicals
  - Compare in vitro with in vivo data
  - Compare in silico with in vitro and in vivo data

Current Status:

- Agreed upon scope of the case study
- Identified case study chemicals to enable ground truthing of the decision tree



EPA United States Environmental Protection Agency

Health Canada www.hc-sc.gc.ca

efsa European Food Safety Authority

EURL ECVAM European Union Reference Laboratory for Alternatives to Animal Testing

European Commission ENVIRONMENT

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Other Accomplishments

- New APCRA logo!!!
- APCRA Website
  - https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra
  - Developing a stand-alone APCRA website (COMING SOON)

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Conceptual Model for APCRA – OECD Interactions

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OECD (e.g., IATA Case Studies)

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Future of APCRA

APCRA will continue to:

- Mature and evolve.
- Be a platform for innovation and idea exchange between regulatory scientists.
- Remain an inter-governmental collaboration.
- Develop new collaborative case studies to address gaps in specific scientific and regulatory needs.
- Identify and address barriers for application of NAMs in a regulatory context.
- Communicate progress on the overall APCRA effort, using periodic public webinars and scientific publications on advances in the science.