Accelerating the Pace of Chemical Risk Assessment (APCRA)

A government to government initiative

Public Webinar March 2020

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APCRA Introduction

Context

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Participants

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Overview of activities

Disclaimer

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Chemicals management systems and testing

Chemicals management systems tend to be based on the utilisation of OECD Guideline studies for classification and risk assessment, which, together with exposure considerations leads to risk management in the supply chain and/or regulatory risk management where appropriate;

To minimise testing, available other information can often be used to build argumentations of weight of evidence and read across, under the specific requirements of each regulation;

For 'simple' endpoints with local effects, the effort to replace these animal studies has been focussed on in-vitro and QSAR, with generally a successful outcome;

For complex (systemic) endpoints, the current animal based approach provides with a surrogate biological system, where all possible effects at clinical level are 'measured', leading to 'POD' for risk assessment and/or classification. Specifically the UN-GHS has been based on the possible outcomes of animal studies.

State of play on industrial chemicals

The "2020 goals", adopted at the 2002 UN World Summit on Sustainable Development, triggered many initiatives, improving safe use of industrial chemicals, including the generation of more data and knowledge;

It is clear that despite efforts made, this challenge is far from being addressed;

For many chemicals on the market(s) in significant volume with expected relevant exposures, information is lacking to robustly conclude on their CMR[1] and/or PBT[2] properties;

The lack of robust prediction tools for these endpoints hampers as well (pro-) active management of emerging priorities, including (avoiding regrettable) substitution.

1) Carcinogenic Mutagenic Reprotoxic
2) Persistent, bio-accumulating and Toxic

New Approach Methods - NAM

NAM was used as a term in a scientific workshop hosted by ECHA "New Approach Methodologies in Regulatory Science" Helsinki, 19–20 April 2016

NAMs were taken in a broad context to include 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 assessment.

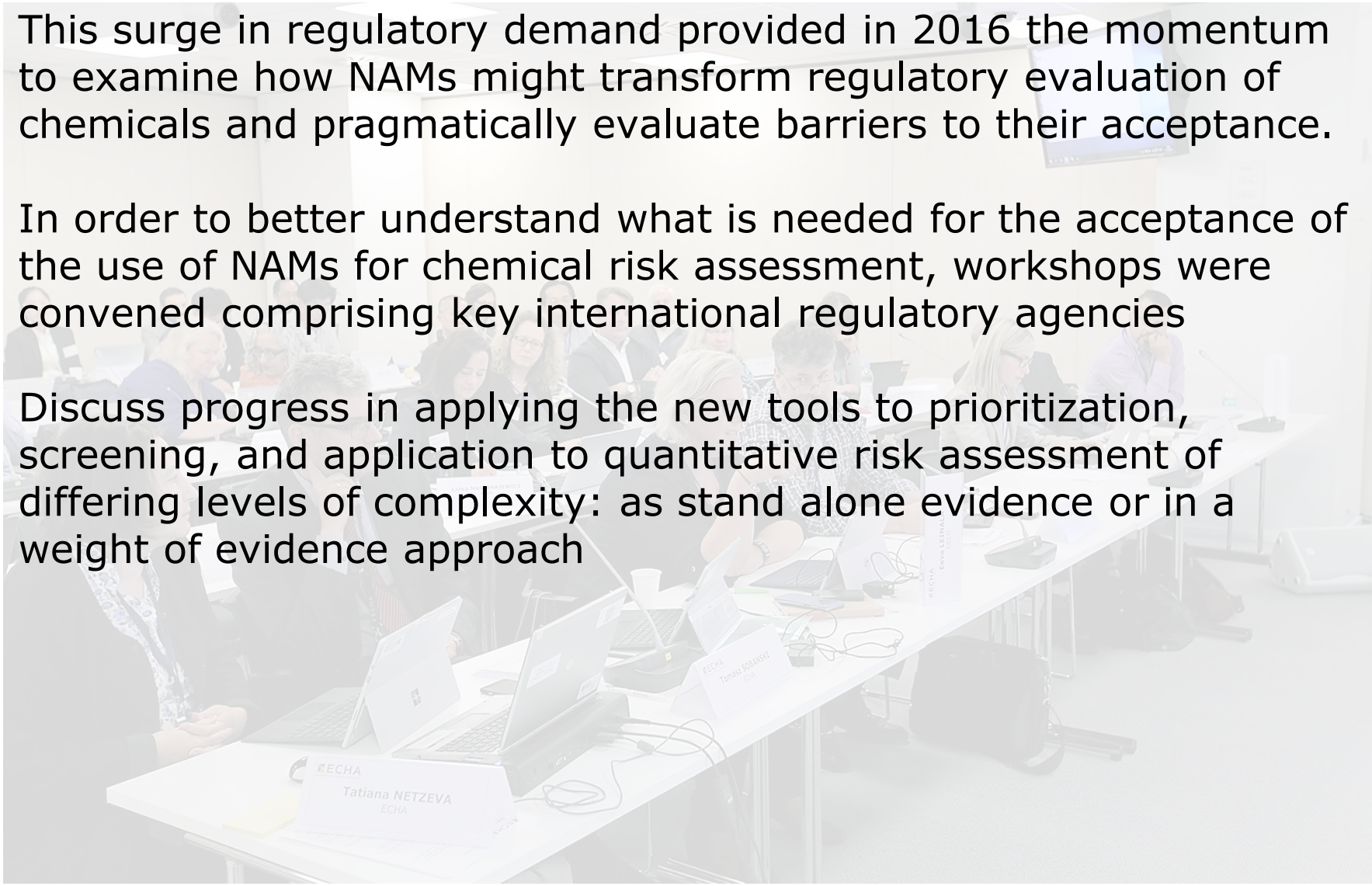
They also include a variety of new testing tools, such as "high-throughput screening" and "high-content methods" e.g. genomics, proteomics, metabolomics; as well as some "conventional" methods that aim to improve understanding of toxic effects, either through improving toxicokinetic or toxicodynamic knowledge for substances.

Momentum

This surge in regulatory demand provided in 2016 the momentum to examine how NAMs might transform regulatory evaluation of chemicals and pragmatically evaluate barriers to their acceptance.

In order to better understand what is needed for the acceptance of the use of NAMs for chemical risk assessment, workshops were convened comprising key international regulatory agencies

Discuss progress in applying the new tools to prioritization, screening, and application to quantitative risk assessment of differing levels of complexity: as stand alone evidence or in a weight of evidence approach



Why is ECHA investing in this?

Ambition: define how New Approach Methods can be used in a regulatory context to enhance the pace of our work, to have better informed, more relevant decisions and ultimately reduce/replace the need for studies on (vertebrate) animals, with a main focus on higher tier human health and environmental 'endpoints'.

What is a "New Approach Method"?

- For ECHA: a method that (potentially) can significantly contribute to fulfil this ambition in terms of:
  - Throughput and/or
  - Robustness and/or;
  - Bringing mechanistic knowledge and/or;
  - Providing appropriate protection levels for human health and Environment.

We are exploring the use of NAM in priority setting, enhancing read-across, integrated into WoE/IATA/DA, and as a 'stand alone' assessment tool.

Accelerating the Pace of Chemical Risk Assessment (APCRA)

What is APCRA?

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.

APCRA
2016
Washington, DC
US

APCRA-2
2017
Helsinki, Finland

APCRA-3
2018
Ottawa, Canada

APCRA-4
2019
Research Triangle Park, NC
US

APCRA-5
2020
Utrecht, Netherlands

Participants

United States: EPA, California EPA, NTP, CPSC, FDA, NIH

Canada: Health Canada, Environment Climate Change Canada

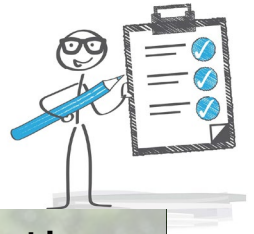
Europe: ECHA, EFSA, JRC, INERIS, RIVM

Asia: Korea – Ministry of the Environment, Japan – Ministry of the Environment & Ministry of Health, Welfare and Labour, Singapore – A*STAR, Taiwan – SAHTECH

Australia: NICNAS

OECD

Goals



- 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.

Goals and Outcomes of First Workshop

- **Hosted by US EPA**
- **Washington, DC (2016)**

- **Focus of the first workshop**
  - Compilation of a master list of chemicals of common international interest for ongoing and future NAM application
  - Identification of potential sources of NAM information and how such information could be shared and exploited
  - Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context and presentation of practical examples
  - Commitment to development and sharing of case studies of mutual interest
- **A total of 10 case studies were originally proposed**

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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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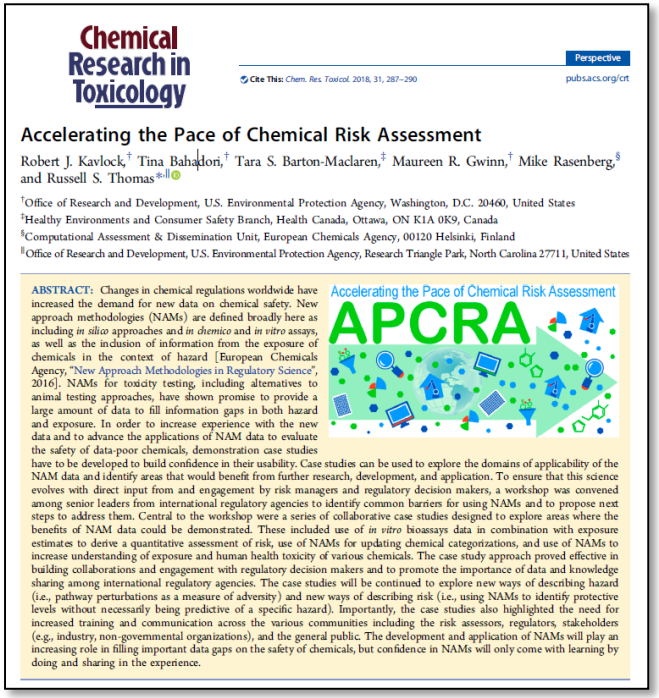
- http://news.bna.com/deln/DELNWB/split_display.adp?fedfid=100707248&vname=dennotallissues&split=0

Goals and Outcomes of Second Workshop

- **Hosted by ECHA**
- **Helsinki FINLAND (2017)**

- **Focus of the second workshop**
  - Identifying and addressing critical data gaps
  - Understanding requirements for acceptance of NAMs by regulators and the public
  - Adding NAMs for exposure analysis
- **A total of 6 case studies were continued**



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.

- https://pubs.acs.org/doi/10.1021/acs.chemrestox.7b00339

Goals and Outcomes of Third Workshop

- **Hosted by Health Canada**
- **Ottawa, ONTARIO (2018)**

- **Focus of the third workshop**
  - Identifying and addressing critical data gaps
  - Increasing understanding of realistic benchmarks for performance of NAMs in different regulatory contexts.
  - Adding NAMs for ecotoxicology analysis
- **A total of 4 new case studies were proposed**

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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.

•https://news.bloombergenvironment.com/environment-and-energy/insight-new-approaches-to-chemical-assessment-a-progress-report

Goals and Outcomes of Fourth Workshop

- **Hosted by US EPA**
- **Research Triangle Park, NC (2019)**

- **Focus of the fourth workshop**
  - Overview of current and new case studies
  - Progress in applying new approach methodologies (NAMs) in different regulatory contexts
  - Integration of NAMs in risk assessment
- **A total of 4 new case studies were proposed**

APCRA Activities

General Requirements for the APCRA Case studies

- must fit the criteria of promoting collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in clear regulatory context.
- include international collaborative case studies on topics of interest to multiple regulatory agencies.
- have largely been communicated through presentations at professional meetings and publications.

APCRA Case Studies

- **Application to Risk Evaluation**
  - Bioactivity as a conservative estimate of PODs
  - Quantitative and qualitative comparison of NAMs and traditional animal toxicity testing for data poor chemicals
  - Use of transcription profiles and primary human liver cells grown as spheroids to address potency and additivity of perfluorinated alkylated substances.
- **Application to Chemical Categorization**
  - Develop NAM profiles based on available data (e.g., high throughput in vitro assay data) for existing chemical categories
  - Evaluate the effectiveness of EcoNAMs, specifically omics technologies used in conjunction with third-wave machine learning, to derive molecular data for mechanism-driven substance grouping..
- **Application to Exposure Evaluation**
  - Use of innovative modeling and GIS approaches by various agencies for assessing lead exposures
  - Triaging chemical exposure data needs and tools for next-generation risk assessment

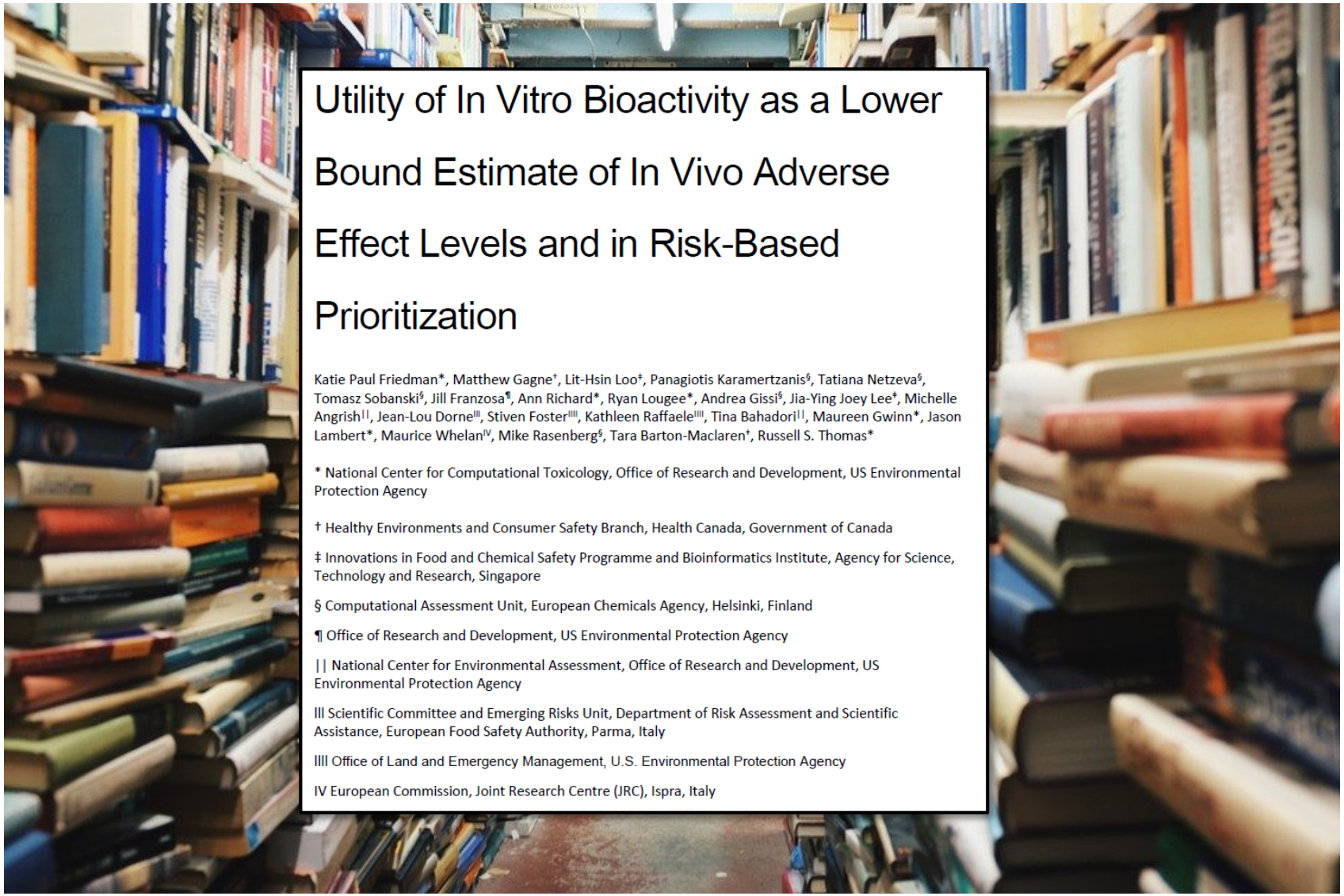
Ongoing APCRA Case Studies

- Prospective Case Study to assess chemicals, using and developing New Approach Methodologies (NAM) –ECHA
- 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
- Revisiting and updating chemical categorizations with new approach methods (NAMs) – US EPA
- Evaluation of Quantitative Structure Use Relationship (QSUR) Models with Industry-Reported Data –US EPA
- Further Exploration of High-Throughput and Traditional Exposure Estimates to Advance NAM and Prioritization Tools for Exposure – Health Canada
- EDC-NAM Categorization – INERIS
- 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
- Substantiating Chemical Categories with Omics-derived Mechanistic Evidence (SuCCess) –ECHA
- 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

New APCRA Case Studies

- In vitro assessment of digestibility and gastrointestinal absorption of nanofibers –European Food Safety Authority
- Investigating the applicability of high throughput transcriptomics data to inform quantitative hazard assessments for ecological species using bioactivity-to-exposure ratios (eco-BER) – US EPA
- A NAM-Based Integrated Approach for Screening Potential Genotoxic Chemicals – Health Canada
- Advanced Threshold of Toxicological Concern (TTC) for priority setting –NICNAS

First Published Joint APCRA Case Study



Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization

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|||| Office of Land and Emergency Management, U.S. Environmental Protection Agency

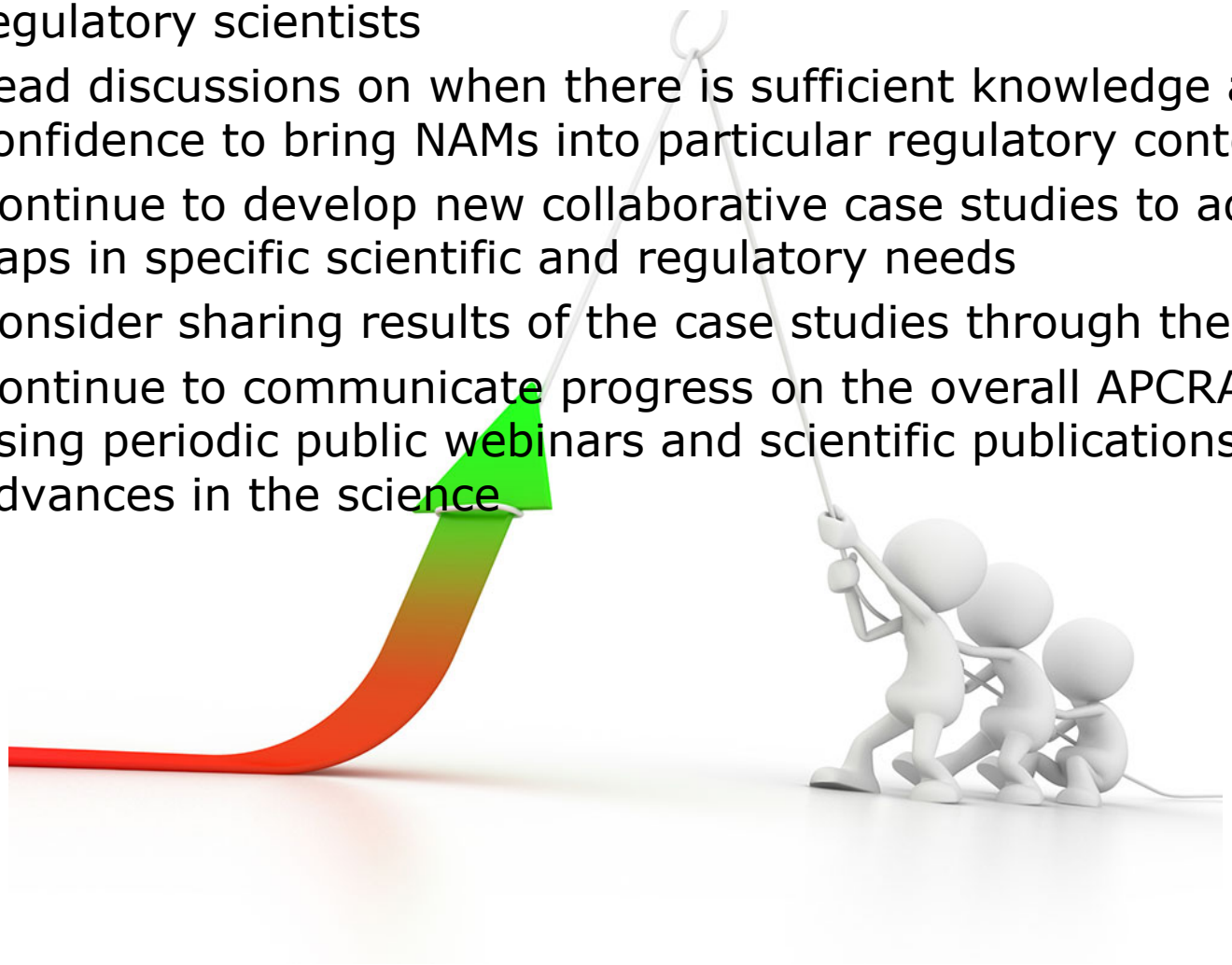
IV European Commission, Joint Research Centre (JRC), Ispra, Italy

•Toxicol Sci. 2019 doi: 10.1093/toxsci/kfz201

Path forward

APCRA will:

- Be a platform for innovation and idea exchange between regulatory scientists
- Lead discussions on when there is sufficient knowledge and confidence to bring NAMs into particular regulatory contexts
- Continue to develop new collaborative case studies to address gaps in specific scientific and regulatory needs
- Consider sharing results of the case studies through the OECD
- Continue to communicate progress on the overall APCRA effort, using periodic public webinars and scientific publications on advances in the science



Next Steps

- APCRA-4 Summary publication
  - In process
- APCRA-4 Public Update
  - Webinar designed to share updates from the October meeting
  - Will be open to public stakeholders
- Fifth APCRA workshop
  - Co-hosted by ECHA and RIVM
  - In conjunction with 11th World Congress on Alternatives and Animals Use in the Life Sciences – August 2020

Conclusions

Regulatory agencies are investing in the possibilities to (further) integrate New Approach Methodologies in their work, in an international collaborative approach, initiated by US EPA.

The bar is high in terms of regulatory decision making (‘legal certainty’), the technical challenges are significant, but there is an ambition to increase the pace of assessments, and ultimately reduce animal testing.

Progress is made by conducting case studies, that trigger focussed discussions which increase the understanding of needs and potential solutions.

Thank you!