EPA Public Access
Author manuscript
Chem Res Toxicol. Author manuscript; available in PMC 2019 July 30.
About author manuscripts | Submit a manuscript

Published in final edited form as:
Chem Res Toxicol. 2018 May 21; 31(5): 287–290. doi:10.1021/acs.chemrestox.7b00339.

Accelerating the Pace of Chemical Risk Assessment

Robert J. Kavlock[1], **Tina Bahadori**[1], **Tara S. Barton-Maclaren**[2], **Maureen R. Gwinn**[1], **Mike Rasenberg**[3], **Russell S. Thomas**[4]

[1]US Environmental Protection Agency, Office of Research and Development, Washington, DC [2]Health Canada, Healthy Environments and Consumer Safety Branch, Ottawa, ON, Canada [3]European Chemicals Agency, Computational Assessment & Dissemination Unit, Helsinki, Finland [4]US Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC

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, in chemico and in vitro assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard[1]. 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, nongovernmental organizations), and the general public. The development and application of NAMs will play an increasing role in filling important

Publisher's Disclaimer: Disclaimer: The views expressed are those of the authors and do not necessarily represent the policies of the US Environmental Protection Agency, Health Canada, or the European Chemicals Agency.

EPA Author Manuscript
EPA Author Manuscript
EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

data gaps on the safety of chemicals, but confidence in NAMs will only come with learning by doing and sharing in the experience.

Graphical Abstract

The modernization of the Toxic Substances Control Act (TSCA), the implementation of EU's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), the next phase of the Canadian Chemicals Management Plan (CMP), and many international chemical management policies and laws have escalated the demand for data on the safety of chemicals. To meet this demand, a variety of new data streams – in hazard, exposure, and dose evaluation - are being considered to augment traditional toxicology data which has mostly relied on animal models. The new data are diverse and include data from high throughput toxicity and toxicokinetic testing, molecular epidemiology, toxicogenomics, exposure science, computational chemistry, and new animal models, among others.

In addition, in the United States, the recent Frank R Lautenberg Chemical Safety for the 21st Century Act amended TSCA by including, among other things, the promotion of the use of alternatives to vertebrate animals under the chemical testing authority. Similarly, REACH and the third phase of the CMP will be integrating new approach methodologies (NAMs) for prioritization and risk assessment activities for data poor chemicals through the use of *in vitro* methods where there is a paucity of data from *in vivo* animal models.

As chemical risk assessment has continued to evolve in response to the shifting toxicity testing paradigm and the introduction of new regulations, it has highlighted areas related to the use of animal studies – they are time consuming and require a large number of resources in order to study just one chemical. Even when available, information from animal studies must be extrapolated to humans with the accompanying uncertainties. There is clearly not enough time or resources to perform traditional animal studies on the high number of data poor chemicals still remaining to be evaluated. A concerted effort has been made to accelerate the pace of chemical risk assessment, with risk assessors in collaboration with research scientists developing ways to more quickly provide information on chemicals' effects. This has provided the opportunity to advance chemical risk assessment to incorporate data from NAMs that are becoming available for thousands of chemicals. Through increased use of NAMs, chemicals can be more quickly screened, allowing resources to be focused on those chemicals that are prioritized either for further testing or for

EPA Author Manuscript EPA Author Manuscript EPA Author Manuscript

more in-depth risk assessment. The use of NAMs has further highlighted the need to share data and approaches and to coordinate resources for chemical prioritization and evaluation.

Given the different regulatory landscapes, scientists/assessors need to work with colleagues across the globe to better understand common barriers and identify opportunities to leverage resources to address these common challenges, together. Along with this increased demand for NAMs data comes the need for sharing of data and knowledge across the regulatory landscape. This surge in scientific interest and regulatory demand provides the momentum to examine how NAMs can contribute to the transformation of the regulatory evaluation of chemicals and pragmatically tackle barriers to acceptance. These barriers include potential limitations and uncertainties of existing technologies and lack of understanding in applying NAMs to address a range of regulatory demands and requirements.[2,3]

Scientists from regulatory agencies from around the world recently met to discuss these issues, in order to identify common barriers and propose next steps to address them. This 2017 Accelerating the Pace of Chemical Risk Assessment (APCRA) workshop, hosted by the European Chemicals Agency, was a follow-up to the original meeting hosted by the US Environmental Protection Agency in September 2016 in Washington, DC, and included scientists from regulatory agencies from the United States, Australia, Japan, Korea, Singapore, Canada and Europe.[a] Central to the 2017 meeting were a series of collaborative case studies designed to address issues proposed at the first meeting in 2016, including: use of *in vitro* bioassays in combination with exposure estimates to derive a quantitative assessment of risk; use of NAMs for updating chemical categorizations; and use of NAMs to better understand exposure and human health toxicity of various chemicals [See Text Box 1]. The primary objective driving the development of these case studies is to advance NAM application to address challenges in chemical evaluation through learning by doing. This practical approach to tackling immediate and pressing assessment needs supports the parallel advancement of innovative approaches to meet regulatory requirements while demonstrating context specific utility in advance of fully mature assays and methods. These case studies are designed to aid in the acceleration of the important application of NAMs to current problems in risk assessment. Case-study and meeting participants focused this effort on the use of NAMs to address existing regulatory challenges in a variety of decision contexts, while acknowledging there are other areas of advancement that may help with some of these issues (e.g., systematic review) and that there are uncertainties that must be considered.

One consistent barrier to the use of NAMs in chemical evaluation is the lack of general acceptance of these new tools and data. Part of this lack of acceptance is likely related to the lack of understanding of these novel approaches and how they could contribute to fulfilling the regulatory needs for decisions on hazard classification and risk assessment, along with a lack of trust in the results due to a perceived lack of validation. In most cases, current use of NAMs has been restricted largely to screening and prioritization of chemicals – that is, being used to determine if a chemical is of concern for a particular endpoint due to activity in a

[a]Overview of the workshop discussion on barriers to NAMs acceptance was presented as a commentary for BNA's Daily Environment Report, Practitioner Insights: "Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious." This commentary discusses many of the barriers to use of NAMs in chemical risk assessment, as well as proposed case studies to help to address them.[4]

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

certain pathway. These chemicals can then be prioritized for further evaluation, either by NAMs or traditional toxicity testing. Moving forward, NAMs will need to be applied for more than just these early steps in the risk assessment process. Importantly, through the case study development and illustrated use of NAMs in a weight-of-evidence context, information is accrued leading to decreased uncertainty relative to a result and increased confidence to answer questions about hazard and risk for regulatory decision making.

Next steps

Workshop discussions focused on three main areas: 1) what are the existing data gaps and what is needed to address them; 2) what is needed to lead to acceptance of NAMs by risk assessors, regulators and the public; and 3) what does the use of NAMs look like for exposure analysis. To help address existing data gaps, case study development can further identify and begin to address the limitations of NAMs. For example, one limitation of NAMs is the lack of metabolic competence of the assays. Research is ongoing to address this, and can inform this data gap and limitation. Future case studies need to explore new ways of describing hazard in ways that NAMs are designed to address such as looking more at whether bioactivity in a certain pathway is predictive of adversity. They also should examine new ways of describing risk - i.e., being protective without the requirement of being predictive. There is also a clear need for better data sharing among agencies and nations. Sharing the data would save on resources, allow for a decrease in duplicative analysis, increase the number of chemicals assessed, and enhance international acceptance. This would require a more standard reporting of results, so they can easily be interpreted across groups.

Increased training and communication are needed to advance acceptance of NAMs by risk assessors, regulators, stakeholders, and the general public. In order to increase confidence in the science, the process, and the product, illustrative case studies will have to be developed and applied to a specific decision context to evaluate the limits of their applicability and robustness. In this vein, it will be critical to build on existing case study efforts and develop new ones by engaging the broader scientific community. These case studies should be fit-for-purpose or proof-of-concept thereby increasing familiarity with the potential uses of NAMs. This approach also serves to increase transparency on how data are generated, analyzed, and reported. Criteria may be required to increase comfort for many with the use of NAMs, as this would give the end users more confidence in the resulting data. To help with engaging the broader scientific community on discussions and advancements on the use NAMs in risk assessment, these collaborative case studies will be shared through presentations and publications. Further, opportunities will be sought to contribute expertise and analyses as applicable to international fora such as the Organisation of Economic Cooperation and Development (OECD).

Similar to hazard evaluations, forward movement on the use of NAMs for exposure will require the establishment of a common vocabulary and a common understanding of how the data represent exposures (e.g, occurrence vs concentration). Exposure NAMs, like data from non-targeted analyses, could be used to better inform screening and prioritization of chemicals by identifying substances that have increased prevalence in the environment.

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

Toxicity can be informed by exposure NAMs used to determine internal dose, and mitigation and prevention strategies can benefit from increasing our understanding of sources and routes of exposure.

Conclusion

Transforming risk assessment through incorporating new techniques and approaches will require a significant leap across a chasm of unknowns and uncertainties, and a commitment to making risk assessments more timely and responsive. The only way to succeed is to work across borders, and include various disciplines and stakeholder groups. The use of NAMs in chemical risk assessment will accelerate the pace by informing data gaps for more chemicals in a shorter time frame. In order to be applied more routinely and move this field forward globally, acceptance is needed for the use of NAMs in risk assessment activities, particularly those applications that are used to inform regulatory decisions. The public will not be adequately served by continuing to perform chemical evaluations based mainly on traditional animal toxicity testing, or epidemiology studies, nor can chemicals continue to be assessed using a substance by substance approach. NAMs also have the potential to bridge the persistent gap in how traditional studies (e.g, epidemiology and animal toxicology) shape risk assessments. Both epidemiology and bioassay methods will remain too costly and time-consuming to be sustainable as the only bases for risk assessment for the tens of thousands of chemicals for which sound regulatory decisions need to be made. Incorporating NAMs into risk assessment practice will require stakeholder groups (e.g., scientists, risk assessors, regulators, industry) to work together to innovate hazard and risk assessment in a way that informs public health protection.

Robert J Kavlock, US Environmental Protection Agency, USA

Dr. Robert J. Kavlock has recently retired following over 40 years at the US Environmental Protection Agency. Prior to his retirement, he was the Acting Assistant Administrator in US EPA’s Office of Research and Development (ORD). Dr. Kavlock was previously the Director of the National Center for Computational Toxicology (NCCT) within ORD, a post he occupied since its founding in 2005. Dr. Kavlock has published more than 200 scientific papers, 16 book chapters, edited three books, and serves on a number of international scientific advisory committees.

Tina Bahadori, US Environmental Protection Agency, USA

Dr. Tina Bahadori is the National Program Director for Human Health Risk Assessment (HHRA) and the Director of the National Center for Environmental Assessment (NCEA) at the US Environmental Protection Agency (EPA). In this role, she continues to work to integrate emerging data, science and tools into risk assessments that inform chemical management decisions. Dr. Bahadori is a member of the Advisory Committee for Environmental Research and Education for the National Science Foundation, and a member of the National Academy of Scienc**es** Chemical Sciences Roundtable.

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

Tara S Barton-Maclaren, Health Canada, Canada

Dr. Tara Barton-Maclaren has over 10 years experience in the field of human health risk assessment and is currently Research Manager of the Emerging Approaches Unit in the Existing Substances Risk Assessment Bureau, Healthy Environments and Consumer Safety Branch of Health Canada. In support of the global transition to 21st Century toxicology, she participates in initiatives under the Organization for Economic Cooperation and Development (OECD) and engages in various scientific collaborations both nationally and internationally in the areas of QSAR, adverse outcome pathways, Integrated Approaches to Testing and Assessment (IATA), and new approaches to support regulatory decision-making.

Maureen R Gwinn, US Environmental Protection Agency, USA

Dr. Maureen Gwinn is currently a Senior Science Advisor in the National Center for Computational Toxicology (NCCT) in the Office of Research and Development (ORD) focusing on research translation of alternative toxicity testing, particularly as it relates to hazard characterization and risk assessment for regulatory decision-making. Previously, Dr. Gwinn worked in the National Center for Environmental Assessment (NCEA) in ORD, where she worked on human health hazard assessments for the Integrated Risk Information System (IRIS) program.

Mike Rasenberg, European Chemicals Agency, European Union

Mr. Mike Rasenberg has over 16 years of professional experience working in the field of chemical regulatory affairs with both governmental bodies and enterprises. Mr. Rasenberg is Head of Unit for Computational Assessment and Dissemination at the European Chemicals Agency (ECHA) since January 2011. Before this, Mr. Rasenberg worked in the area international chemicals management, with the European Commission, Chemical Industry, industry associations and as a consultant.

Russell S Thomas, US Environmental Protection Agency, USA

Dr. Russell Thomas is the director of the National Center for Computational Toxicology at the US EPA. He has been at US EPA since 2013. The Center is researching new, more efficient ways to evaluate the safety of chemicals, particularly in assessing chemicals for human health effects. Prior to coming to the US EPA, Dr. Thomas was the director of the Institute for Chemical Safety Sciences at The Hamner Institutes for Health Sciences and worked in the biotech and biopharmaceutical industry.

References

1. ECHA (European Chemicals Agency). (2016) New Approach Methodologies in Regulatory Science. https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf/a2087434-0407-4705-9057-95d9c2c2cc57. Accessed February 14, 2018.
2. Dong Z, Liu Y, Duan L, Bekele D, Naidu R (2015) Uncertainties in human health risk assessment of environmental contaminants: A review and perspective. Environ Int 85, 120–132. [PubMed: 26386465]
3. NASEM (National Academies of Sciences, Engineering, and Medicine). (2017) Using 21st Century Science to Improve Risk-Related Evaluations. Washington, DC: National Academies Press (US) 10.17226/24635.

4. Kavlock RJ (2016) BNA Daily Environment Report, Practitioner Insights: “Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious”; http://news.bna.com/deln/DELNWB/split_display.adp?fedfid=100707248&vname=dennotallissues&split=0. Accessed February 14, 2018.

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

TEXT BOX

Ongoing Case Studies

Advancing methodology

- Bioactivity as a conservative estimate of no- and low effect levels in traditional animal studies
  - Retrospective comparison of point of departure (POD) from NAMs (e.g., high-throughput in vitro bioactivity data) to POD from traditional studies
  - Evaluate the bioactivity-to-exposure ratio (BER) as a means for risk-based prioritization
- Quantitative and qualitative comparison of NAMs and traditional animal toxicity testing for data poor chemicals
  - Prospective case study to evaluate the qualitative 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

Understanding key chemical classes

- 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 pathways of interest
- Understanding chemical categorizations
  - Develop NAM profile based on available data (e.g., high-throughput 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 ahead of time

Exposure

- Triaging chemical exposure data needs and tools for next-generation risk assessment
  - Including new approach methodologies for exposure, including computational exposure science and *in silico* approaches

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

- Expanding use of high-throughput exposure methods, like non-targeted analysis and quantitative structure-activity relationship (QSAR) models

- Use of new exposure modeling for systematic analysis of lead exposures
  - Using lead 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 toxicity assessments and health-based decision-making