Interagency Coordinating Committee on the Validation of Alternative Methods

A Year in Review: ICCVAM Accomplishments in Advancing the 3Rs

Anna Lowit, PhD
U.S. EPA/OPP

SACATM Meeting
September 28-29, 2021

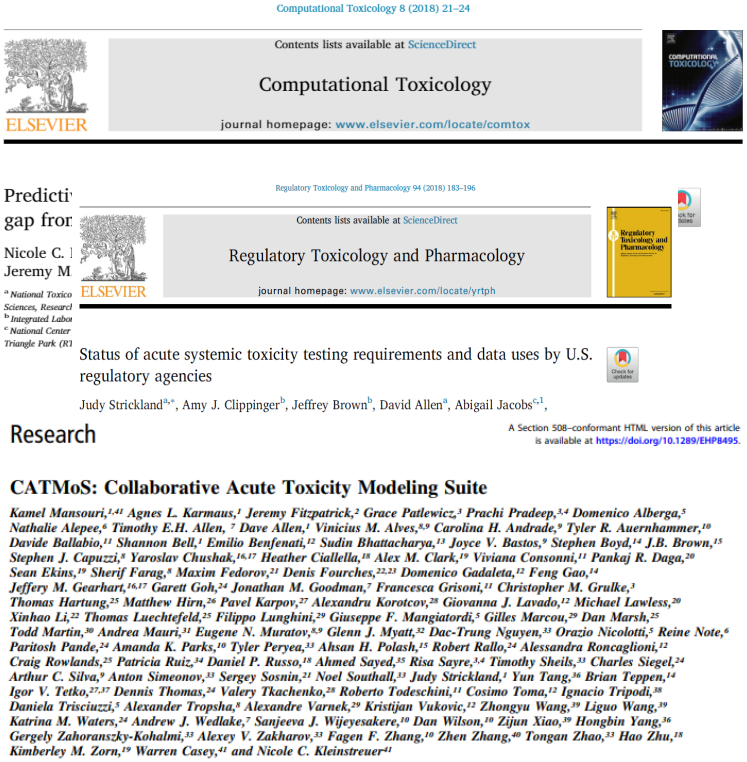
Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation Energy
Department of Veterans Affairs Office of Research and Development • Environmental Protection Agency • Food and Drug Administration
National Institute for Occupational Safety and Health • National Institutes of Health • National Cancer Institute
National Institute of Environmental Health Sciences • National Institute of Standards and Technology • National Library of Medicine
Occupational Safety and Health Administration

Outline

- ICCVAM Workgroups
  - Acute Toxicity
  - Ecotoxicity
  - In Vitro to In Vivo Extrapolation
  - Nanomaterials
  - Read Across
  - Validation
- ICCVAM Communities of Practice
- Society of Toxicology Participation
- ICCVAM Public Forum

Acute Toxicity Testing

- Evaluate the usefulness of acute oral LD50 data for classifying dermal systemic hazard of potential toxicants such as pesticides, industrial chemicals, chemical warfare agents, and household chemicals
  - Complete – for pesticide formulations and active ingredients; EPA published waiver guidance for formulations in 2016 and for technical chemicals in 2020
- Evaluate in vitro/in silico approaches for predicting acute systemic toxicity
  - Modeling workshop convened – workshop report published (Kleinstreuer et al. 2018)
  - Acute oral toxicity in silico models – CATMoS (Mansouri et al. 2021); model predictions for ICCVAM agencies
  - Variability analysis of the in vivo oral test method (manuscript in NIEHS clearance)
  - Acute inhalation toxicity – evaluating suitability of available acute inhalation toxicity data for modeling
- GHS additivity formula evaluation for acute systemic toxicity tests
  - Manuscript submitted to Regulatory Toxicology and Pharmacology
- Publish a scoping document that outlines the current requirements and testing needs for U.S. and international regulatory authorities
  - Complete (Strickland et al. 2018)



Computational Toxicology 8 (2018) 21–24

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

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Regulatory Toxicology and Pharmacology 94 (2018) 183–196

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Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Predicti
gap fror
Nicole C.
Jeremy M

Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies

Judy Strickland, Amy J. Clippinger, Jeffrey Brown, David Allen, Abigail Jacobs,

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP8495.

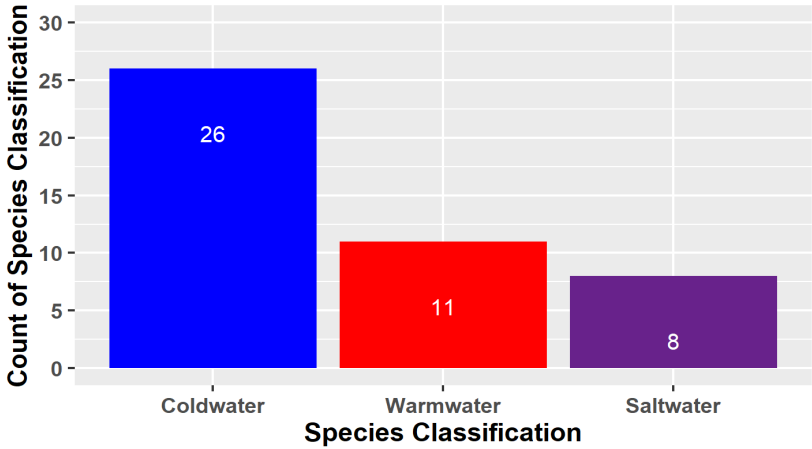
CATMoS: Collaborative Acute Toxicity Modeling Suite

Kamel Mansouri, Agnes L. Karmaus, Jeremy Fitzpatrick, Grace Patlewicz, Prachi Pradeep, Domenico Alberga, Nathalie Alepee, Timothy E.H. Allen, Dave Allen, Vinicius M. Alves, Carolina H. Andrade, Tyler R. Auernhammer, Davide Ballabio, Shannon Bell, Emilio Benfenati, Sudin Bhattacharya, Joyce V. Bastos, Stephen Boyd, J.B. Brown, Stephen J. Capuzzi, Yaroslav Chushak, Heather Ciallella, Alex M. Clark, Viviana Consonni, Pankaj R. Daga, Sean Ekins, Sherif Farag, Maxim Fedorov, Denis Fourches, Domenico Gadaleta, Feng Gao, Jeffery M. Gearhart, Garett Goh, Jonathan M. Goodman, Francesca Grisoni, Christopher M. Grulke, Thomas Hartung, Matthew Hirn, Pavel Karpov, Alexandru Korotcov, Giovanna J. Lavado, Michael Lawless, Xinhao Li, Thomas Luechtefeld, Filippo Lunghini, Giuseppe F. Mangiatordi, Gilles Marcou, Dan Marsh, Todd Martin, Andrea Mauri, Eugene N. Muratov, Glenn J. Myatt, Dac-Trung Nguyen, Orazio Nicolotti, Reine Note, Paritosh Pande, Amanda K. Parks, Tyler Peryea, Ahsan H. Polash, Robert Rallo, Alessandra Roncaglioni, Craig Rowlands, Patricia Ruiz, Daniel P. Russo, Ahmed Sayed, Risa Sayre, Timothy Sheils, Charles Siegel, Arthur C. Silva, Anton Simeonov, Sergey Sosnin, Noel Southall, Judy Strickland, Yun Tang, Brian Teppen, Igor V. Tetko, Dennis Thomas, Valery Tkachenko, Roberto Todeschini, Cosimo Toma, Ignacio Tripodi, Daniela Trisciuzzi, Alexander Tropsha, Alexandre Varnek, Kristijan Vukovic, Zhongyu Wang, Liguo Wang, Katrina M. Waters, Andrew J. Wedlake, Sanjeeva J. Wijeyesakere, Dan Wilson, Zijun Xiao, Hongbin Yang, Gergely Zahoranszky-Kohalmi, Alexey V. Zakharov, Fagen F. Zhang, Zhen Zhang, Tongan Zhao, Hao Zhu, Kimberley M. Zorn, Warren Casey, and Nicole C. Kleinstreuer

Ecotoxicity Testing

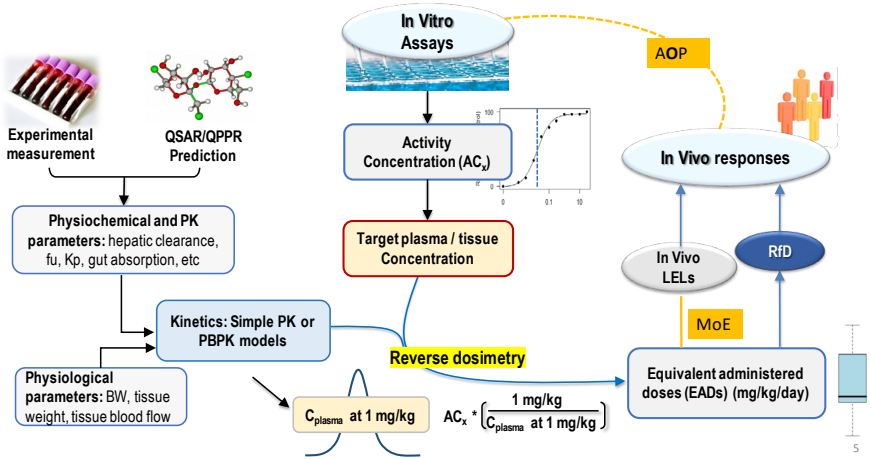
- ICCVAM Agency needs manuscript in progress
  - Identify ecotoxicological test data requirements as they relate to agency/ departmental registration and regulation of chemicals and their use
  - Identify ecotoxicological research and monitoring activities as they relate to agency/departmental mission and programmatic goals
  - Identify endpoints needed by each federal agency and commonalities and differences between agencies
  - *More info from Jessica Leet (DoI) coming up in the next session*

- Identify one or more New Alternative Methods (NAMs) that can potentially be used alone or in combination to reduce, refine, or replace the acute fish toxicity test (Manuscript in progress)
  - Characterize the identified methods
  - Determine criteria that are important to regulatory agencies when considering replacement methods for acute fish toxicity
  - *More info from Natalia Garcia-Reyero (DoD) coming up in the next session*



In Vitro to In Vivo Extrapolation

- Conduct literature searches for current IVIVE methods, models, and case studies; catalog open source and commercially available IVIVE models and software tools (Manuscript in progress)
- Determine specific risk assessment purposes that can be achieved with the currently available approaches, and identify gaps (Included in the manuscript in progress)
- Identify case studies to demonstrate utility and applicability of IVIVE to the needs of risk assessors. (Included in the manuscript in progress)
- Ensure international harmonization on the use and application of IVIVE through ICATM. (Ongoing coordination with OECD)



Nanomaterials Testing

- Identify agency requirements and needs for nanomaterial toxicology testing (Requirements collated; Manuscript submitted for publication)
- Identify other Federal and International efforts in this area (Included in manuscript)
- Work with ICATM partners to identify international regulatory requirements for nanomaterial toxicity testing (Included in manuscript)
- Identify the extent to which agencies accept alternatives to animal testing (i.e., in vitro, physicochemical, nanomaterial grouping) to fulfill regulatory requirements for nanomaterial toxicity testing and if agencies require modifications to standard toxicological methods for use with nanomaterials (Included in manuscript)

U.S. Federal Agency Interests and Recommendations for New Approach Methodologies for Nanomaterials

Elijah J. Petersen[1*]; Patricia Ceger[2*]; Jayme Coyle[3]; David Allen[2]; Raymond Derk[3]; Natalia Garcia-Reyero[4]; John Gordon[5]; Nicole Kleinstreuer[6]; Joanna Matheson[4]; Danielle McShan[7]; Bryant C. Nelson[1]; Anil K. Patri[8]; Penelope Rice[9]; Liying Rojanasakul[3]; Abhilash Sasidharan[10]; Louis Scarano[10]; Xiaoqing Chang[2**]

Draft submitted to ALTEX

Read Across Approaches

- Develop and implement a plan for ICCVAM members to build capacity in the development and application of “read-across” approaches
- Create a catalog of ongoing read-across experiences and needs across the different Agencies to highlight the different decision contexts of interest. (Patlewicz et al. 2019)
- Create a catalog of existing read-across resources (including existing technical guidance and software tools). (Patlewicz et al. 2019)
- Develop a compendium of member agency read-across case studies and use it as a basis to inform guiding principles for different read-across decision contexts. (see next slide)
- Demonstrate impact of the guiding principles identified by facilitating the initiation and completion of a read-across case study presented in an internal agency document. (Complete, feedback on CPSC draft plan for OFR class-based Risk Assessment)

Regulatory Toxicology and Pharmacology 106 (2019) 197–209

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Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Exploring current read-across applications and needs among selected U.S. Federal Agencies

Grace Patlewicz[a,*], Lucina E. Lizarraga[b], Diego Rua[c], David G. Allen[d], Amber B. Daniel[d], Suzanne C. Fitzpatrick[e], Natàlia Garcia-Reyero[f], John Gordon[g], Pertti Hakkinen[h], Angela S. Howard[d], Agnes Karmaus[d], Joanna Matheson[g], Moiz Mumtaz[i], Andrea-Nicole Richarz[j], Patricia Ruiz[i], Louis Scarano[k], Takashi Yamada[l], Nicole Kleinstreuer[m]

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[h] National Library of Medicine, 6707 Democracy Blvd., Bethesda, MD, 20892, USA
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[j] European Commission, Joint Research Centre (JRC), Ispra, Italy
[k] Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC, 20460, USA
[l] Division of Risk Assessment, Biological Safety Research Center, National Institute of Health Sciences, 3-25-26, Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, 210-9501, Japan
[m] National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709, USA

ICCVAM Read Across Case Studies

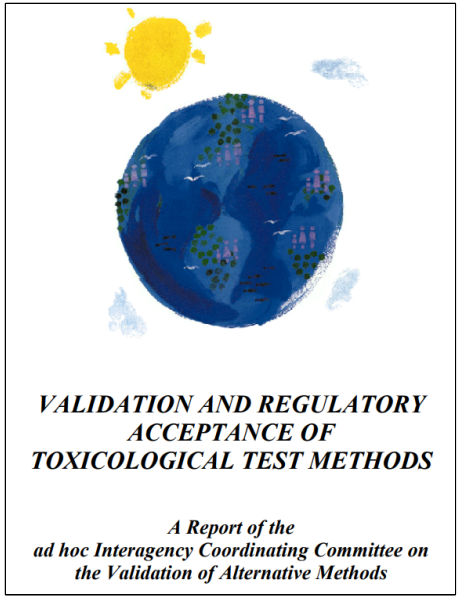
- Case Study Submitted by FDA "**Updates to the Cramer et al. Decision Tree and the Threshold of Toxicological Concern: the Expanded Decision Tree and Its Use as a Read-Across Tool**" Szabina Stice
- Case Study Submitted by "**EPA Revisiting and updating chemical groupings with new approach methodologies"** Dan Chang
- Presentation from CPSC: Draft Plan **"Assessing the Risks of Organohalogen Flame Retardants (OFRs): A Class Approach"** Mike Babich

ICCVAM Validation Workgroup (VWG)

ICCVAM Sponsor Agencies: CPSC, NIST, FDA

- Update ICCVAM report on development and validation of alternative methods (i.e., “VALIDATION AND REGULATORY ACCEPTANCE OF TOXICOLOGICAL TEST METHODS” originally published in 1997).

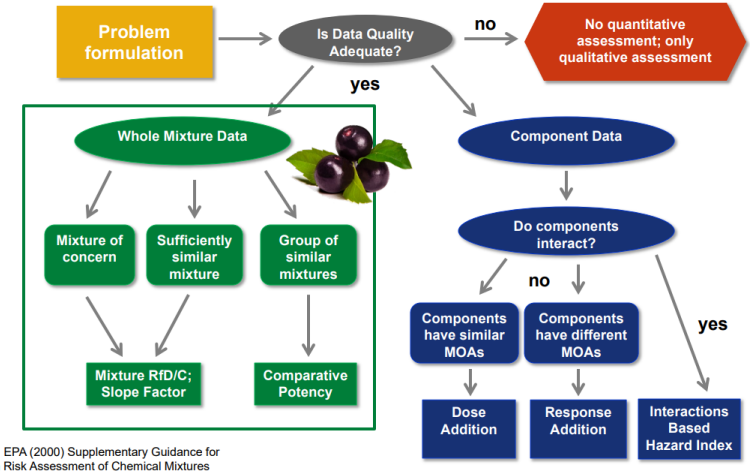
- This process will include but is not limited to:
  - Developing and evaluating flexible practices that consider context of use to build confidence in new methods.
  - Seeking to align validation approaches such that international harmonization can be supported.
  - Pointing to other well-established validation documents for more context-specific information regarding validation (e.g., GIVIMP, OECD GD34, GD69 on QSAR Validation, FDA Guidance for Industry).
  - Evaluating guidance document(s) outlining best practices.
  - Examining best practices for quality and quality systems development.
- “Living document” that will be updated as needed



ICCVAM Communities of Practice: Non-animal Approaches for Mixtures Assessment

- Applying In Vitro Approaches to Understand Complex Mixtures in Assessing Botanical Safety
  - Cynthia Rider, Ph.D., NTP/NIEHS
- Exploring Mechanistic Toxicity of Mixtures Using PBPK Modeling and Computational Systems Biology
  - Patricia Ruiz, Ph.D., Office of Innovation and Analytics, ATSDR
- Mining Potential Chemical Co-exposures from Consumer Product Purchasing and Ingredient Data
  - Kristin Isaacs, Ph.D., Office of Research and Development, EPA
- Approximately 600 registered, 390 attendees
- US Government (state and federal), commercial, academia, NGO, international (Canada, Czech Rep, EU, Finland, France, Germany, Japan, Neth, UK)

Mixtures risk assessment framework



Adapted from U.S. EPA (2000) Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures

https://ntp.niehs.nih.gov/go/commprac-2021

SOT Participation

- Two CE Courses
- Seven Workshops/Symposia
- 19 poster presentations

ICCVAM Committee Activities

ICCVAM Committee member names are indicated in **boldface** in author lists.

- Roundtable Session: The Future of Uncertainty Factors with In Vitro Studies Using Human Cells
- Poster Session: Computational Toxicology I
- Poster Session: Risk Assessment
- Symposium Session: Mind the Gap: Finding Practical Ways to Fast-Track the Future of Animal-Free Toxicology Testing
- Poster Session: Computational Toxicology II
- Poster Session: DNA Damage and Repair
- Poster Session: Alternatives to Mammalian Models I
- Poster Session: Alternatives to Mammalian Models II

https://ntp.niehs.nih.gov/go/niceatm-sot21

ICCVAM Public Forum (May 27, 2021)

- ICCVAM's goals include promotion of national and international partnerships between governmental and nongovernmental groups, including academia, industry, advocacy groups, and other key stakeholders.
- To foster these partnerships, ICCVAM holds annual public forums to share information and facilitate direct communication of ideas and suggestions from stakeholders.
- Representatives of 9 different ICCVAM member agencies described activities both to advance new approaches to safety testing of chemicals and medical products and to reduce the amount of testing required.
- Over 160 attendees
- Public comments – 4 written, 9 in person
- A video recording is available on the meeting website, where the agenda, presentations, and copies of public comments provided can also be found.

https://ntp.niehs.nih.gov/go/iccvamforum-2021