Interagency Coordinating Committee on the Validation of Alternative Methods

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

John Gordon, PhD
U.S. CPSC
SACATM Meeting
September 21-22, 2022

The comments in this presentation are those of ICCVAM. They have not been reviewed or approved by, and may not necessarily reflect the views of any federal agency.

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
  - Consideration of Alternative Methods
  - Ecotoxicity
  - In Vitro to In Vivo Extrapolation
  - Nanomaterials
  - 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; https://doi.org/10.1016/j.comtox.2018.08.002)
  - Acute oral toxicity in silico models – CATMoS (Mansouri et al. 2021; https://doi.org/10.1289/EHP8495); model predictions for ICCVAM agencies
  - Variability analysis of the in vivo oral test method (manuscript published – Karmaus et al. 2022; https://doi.org/10.1093/toxsci/kfac042)
  - Acute inhalation toxicity – finalizing available acute inhalation toxicity dataset for modeling
- GHS additivity formula evaluation for acute systemic toxicity tests
  - Manuscript published – Hamm et al. 2021; https://doi.org/10.1016/j.yrtph.2021.105007
- Publish a scoping document that outlines the current requirements and testing needs for U.S. and international regulatory authorities
  - U.S. published (Strickland et al. 2018; https://doi.org/10.1016/j.yrtph.2018.01.022)
  - International in progress

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Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

Jon Hamm [a,*], David Allen [a], Patricia Ceger [a], Tara Flint [b], Anna Lowit [b], Lindsay O'Dell [b], Jenny Tao [b], Nicole Kleinstreuer [c]

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[b] Office of Pesticide Programs, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave, NW, Washington, DC, 20460, USA
[c] 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

OXFORD SOT Society of Toxicology academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 188(1), 2022, 34–47

https://doi.org/10.1093/toxsci/kfac042
Advance Access Publication Date: 15 April 2022
Research article

Evaluation of Variability Across Rat Acute Oral Systemic Toxicity Studies

Agnes L. Karmaus,* Kamel Mansouri,† Kimberly T. To,* Bevin Blake,†,1 Jeremy Fitzpatrick,‡,2 Judy Strickland,* Grace Patlewicz,‡ David Allen,* Warren Casey,† and Nicole Kleinstreuer †,3

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ICCVAM Consideration of Alternative Methods Workgroup (CAMWG) Charges

ICCVAM Sponsor Agencies: USDA, NIEHS, DOD

- Work with stakeholders to publish a white paper on approaches that could potentially be used to foster the consideration and use of NAMs to replace or reduce live animal use in painful/distressful procedures or refine the work so it is less painful/distressful by organizations currently using animals for testing.
  - Focused discussions ongoing to hear from multiple stakeholders within the toxicology testing community on their experience with the use of NAMs and other alternative methods.
  - The goal is to address various aspects of using NAMs such as availability, validity, barriers, funding opportunities, etc. to better understand how to foster more serious consideration and utility of NAMs.
- Foster collaborations with authorities outside of the U.S. to share ideas and progress to promote greater harmonization for considering NAMs.
- Refer the community to available grants devoted to the development of alternatives to live animal use.
- Identify/improve communication efforts/opportunities that help promote the use of NAMs.
- Where appropriate and feasible, encourage agencies to promote avenues where NAMs can be better considered and leveraged (i.e., suggestions to encourage consideration, adoption, and best practices regarding NAMs).
- ***More on this agenda item later***

Ecotoxicity Testing

- ICCVAM Agency's needs manuscript published (Ceger et al. 2022; https://doi.org/10.1016/j.yrtph.2022.105195)
  - 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

- 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)
  - Prioritized based on potential huge impact on animal use (see figure at right)
  - Characterize the identified methods
  - Determine criteria that are important to regulatory agencies when considering replacement methods for acute fish toxicity
  - Manuscript in progress

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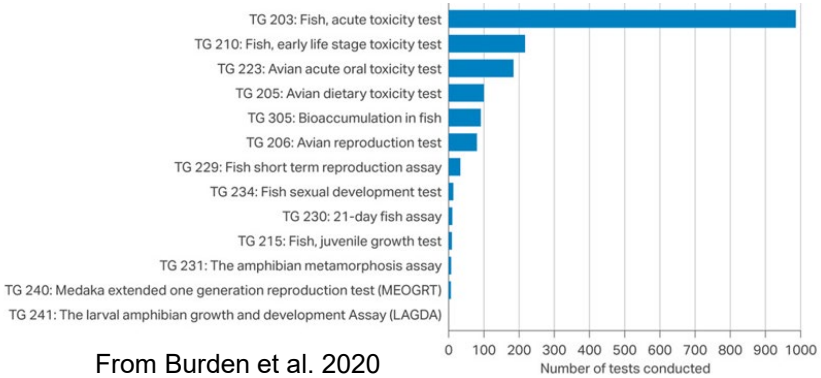
journal homepage: www.elsevier.com/locate/yrtph

Current ecotoxicity testing needs among selected U.S. federal agencies

Patricia Ceger [a,*], Natalia Garcia-Reyero Vinas [b], David Allen [a], Elyssa Arnold [c,1], Raanan Bloom [d], Jennifer C. Brennan [e,2], Carol Clarke [p], Karen Eisenreich [e], Kellie Fay [e], Jonathan Hamm [a], Paula F.P. Henry [g], Katherine Horak [h], Wesley Hunter [i], Donna Judkins [c,3], Patrice Klein [f], Nicole Kleinstreuer [j], Kara Koehrn [e], Carlie A. LaLone [k], James P. Laurenson [d], Jessica K. Leet [l], Anna Lowit [c], Scott G. Lynn [c], Teresa Norberg-King [k,4], Edward J. Perkins [b], Elijah J. Petersen [m], Barnett A. Rattner [n], Catherine S. Sprankle [a], Thomas Steeger [c], Jim E. Warren [f], Sarah Winfield [o], Edward Odenkirchen [c,5]



From Burden et al. 2020

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 published in Toxics – **cover feature!**)
- Determine specific risk assessment purposes that can be achieved with the currently available approaches, and identify gaps (Included in manuscript)
- Identify case studies to demonstrate utility and applicability of IVIVE to the needs of risk assessors. (Included in manuscript)
- Ensure international harmonization on the use and application of IVIVE through ICATM. (Ongoing coordination with OECD)

toxics
MDPI

Review

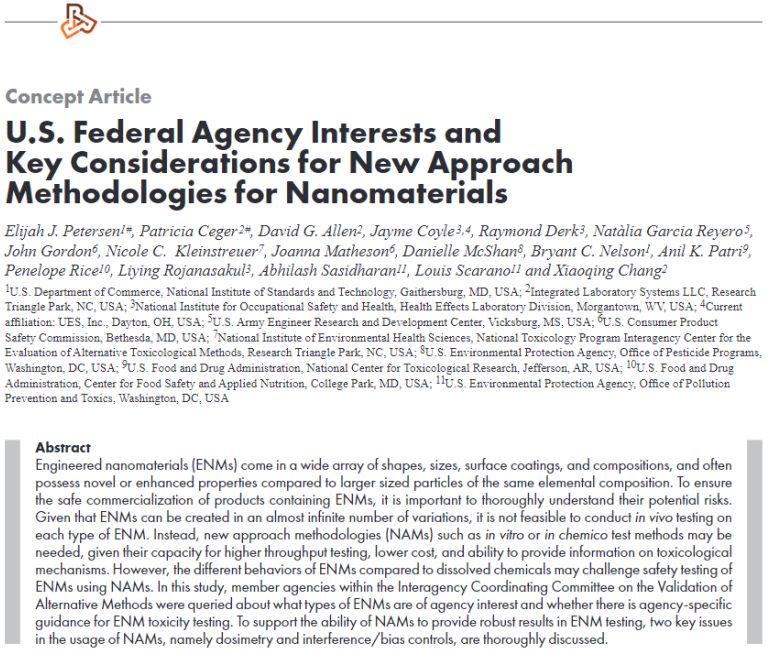
IVIVE: Facilitating the Use of *In Vitro* Toxicity Data in Risk Assessment and Decision Making

Xiaoqing Chang [1,†], Yu-Mei Tan [2,†], David G. Allen [1], Shannon Bell [1], Paul C. Brown [3], Lauren Browning [1,‡], Patricia Ceger [1], Jeffery Gearhart [4,§], Pertti J. Hakkinen [5,§], Shruti V. Kabadi [6], Nicole C. Kleinstreuer [7], Annie Lumen [8,‖], Joanna Matheson [9], Alicia Paini [10,¶], Heather A. Pangburn [11], Elijah J. Petersen [12], Emily N. Reinke [13], Alexandre J. S. Ribeiro [3,**], Nisha Sipes [14], Lisa M. Sweeney [15], John F. Wambaugh [14], Ronald Wange [3], Barbara A. Wetmore [14] and Moiz Mumtaz [16,*]

Toxics 2022, 10, 232. https://doi.org/10.3390/toxics10050232

Nanomaterials Testing

- Identify agency requirements and needs for nanomaterial toxicology testing (Requirements collated; Manuscript published in ALTEX)
- 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)
- Workgroup charges completed - converted to an Expert Group



Concept Article

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

Elijah J. Petersen[1#], Patricia Ceger[2#], David G. Allen[2], Jayme Coyle[3,4], Raymond Derk[3], Natàlia Garcia Reyero[5], John Gordon[6], Nicole C. Kleinstreuer[7], Joanna Matheson[6], Danielle McShan[8], Bryant C. Nelson[1], Anil K. Patri[9], Penelope Rice[10], Liying Rojanasakul[3], Abhilash Sasidharan[11], Louis Scarano[11] and Xiaoqing Chang[2]

[1]U.S. Department of Commerce, National Institute of Standards and Technology, Gaithersburg, MD, USA; [2]Integrated Laboratory Systems LLC, Research Triangle Park, NC, USA; [3]National Institute for Occupational Safety and Health, Health Effects Laboratory Division, Morgantown, WV, USA; [4]Current affiliation: UES, Inc., Dayton, OH, USA; [5]U.S. Army Engineer Research and Development Center, Vicksburg, MS, USA; [6]U.S. Consumer Product Safety Commission, Bethesda, MD, USA; [7]National Institute of Environmental Health Sciences, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, Research Triangle Park, NC, USA; [8]U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC, USA; [9]U.S. Food and Drug Administration, National Center for Toxicological Research, Jefferson, AR, USA; [10]U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, College Park, MD, USA; [11]U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, USA

Abstract

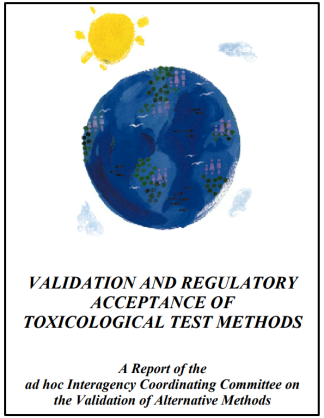
Engineered nanomaterials (ENMs) come in a wide array of shapes, sizes, surface coatings, and compositions, and often possess novel or enhanced properties compared to larger sized particles of the same elemental composition. To ensure the safe commercialization of products containing ENMs, it is important to thoroughly understand their potential risks. Given that ENMs can be created in an almost infinite number of variations, it is not feasible to conduct *in vivo* testing on each type of ENM. Instead, new approach methodologies (NAMs) such as *in vitro* or *in chemico* test methods may be needed, given their capacity for higher throughput testing, lower cost, and ability to provide information on toxicological mechanisms. However, the different behaviors of ENMs compared to dissolved chemicals may challenge safety testing of ENMs using NAMs. In this study, member agencies within the Interagency Coordinating Committee on the Validation of Alternative Methods were queried about what types of ENMs are of agency interest and whether there is agency-specific guidance for ENM toxicity testing. To support the ability of NAMs to provide robust results in ENM testing, two key issues in the usage of NAMs, namely dosimetry and interference/bias controls, are thoroughly discussed.

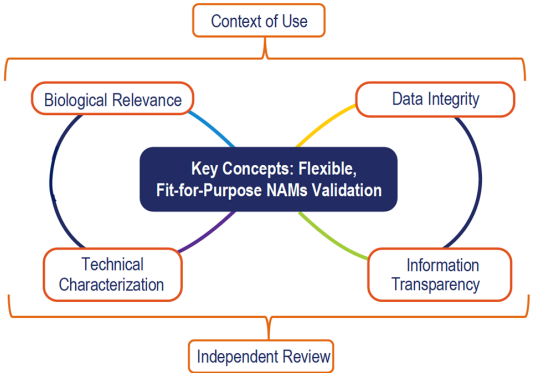
ALTEX 39(2):183-206. https://doi.org/10.14573/altex.2105041.

ICCVAM Validation Workgroup (VWG)

ICCVAM Sponsor Agencies: CPSC, NIST, FDA

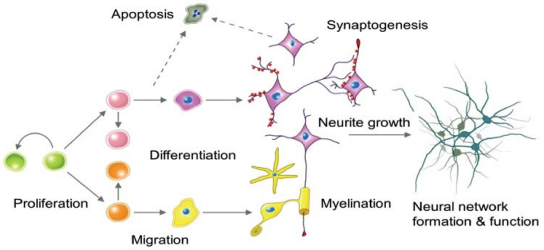
- Update ICCVAM report on development and validation of alternative methods (i.e., "Validation and Regulatory Acceptance of Toxicological Test Methods" originally published in 1997).
- This process includes but is not limited to:
  - Developing and evaluating flexible practices that consider context 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
- Will serve as a resource for U.S. federal agencies and stakeholders seeking to establish confidence in new approaches that address the 3Rs
- ***More on this agenda item later***





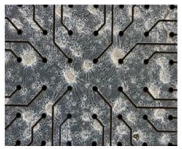
ICCVAM Communities of Practice: New Approach Methodologies to Assess (Developmental) Neurotoxicity

- Developmental Neurotoxicity Assessment Using In Vitro Assays
  - Helena Hogberg, Ph.D., DNTP/NIEHS
- Phenotype-based Mechanistic Studies for the Assessment of Drug Safety and Drug-drug Interactions in Zebrafish: Efficacy of Dietary Supplements
  - Jyotshnabala Kanungo, Ph.D., National Center for Toxicological Research, FDA
- Approximately 350 attendees (535 registered)
- US Government (state and federal), commercial, academia, government, NGO, international (22 countries from 5 different continents)

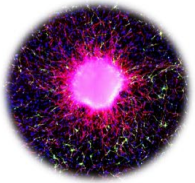


Cell lines, primary cells, stem cells, mainly human derived

2-D assays



3D- Neurospheres



Zebrafish

https://ntp.niehs.nih.gov/go/commprac-2022

SOT Participation

- One CE Course and one satellite meeting
- Six Workshops/Symposia/ Roundtables
- 18 poster presentations

ICCVAM Committee Activities

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

- Poster Session: PFAS I
- Poster Session: Reproductive and Developmental Toxicology I
- Poster Session: Food Safety/Nutrition
- Poster Session: Air Pollution Toxicology II
- Poster Session: DNA Damage and Repair
- Poster Session: Biological Modeling
- Roundtable Session: Tg.rasH2 Positive Controls: Added Value or No Longer Necessary?
- Poster Session: Alternatives to Mammalian Models I

https://ntp.niehs.nih.gov/go/niceatm-sot22

ICCVAM Public Forum (May 26-27, 2022)

- 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 eight 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 100 attendees
- Public comments – five written, five 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-2022