Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM Workgroup Updates

David Allen, PhD

ICCVAM Public Forum
September 18-19, 2023

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
  - PFAS

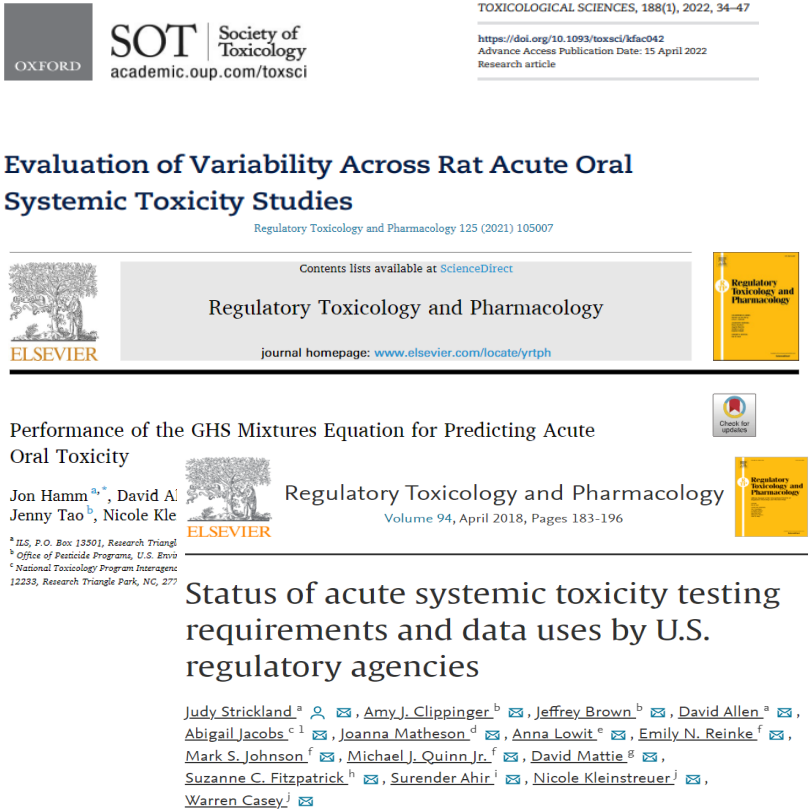
Acute Toxicity Testing

Complete – oral and dermal systemic toxicity

- 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)
- 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 submitted to Current Reviews in Toxicology

Ongoing - inhalation toxicity

- Database of LC50s being finalized for model development and variability analyses



Consideration of Alternative Methods

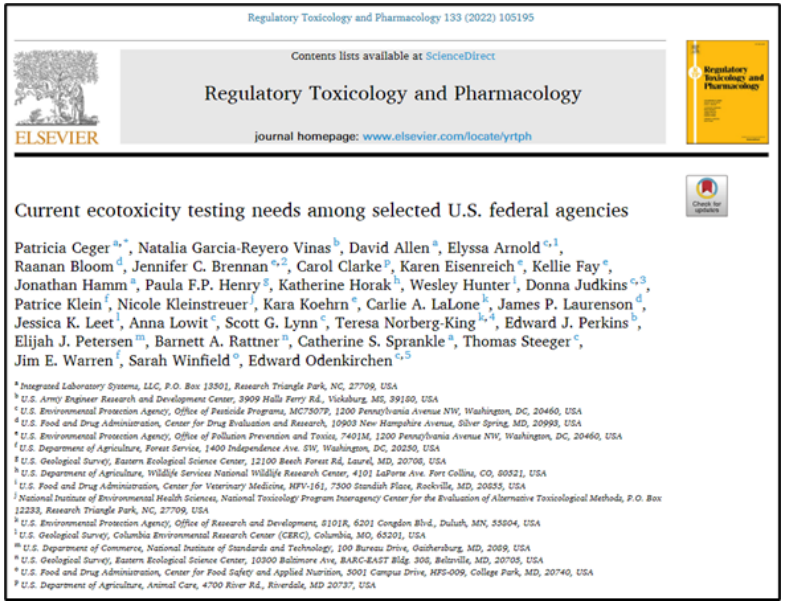
- Working with stakeholders to develop a catalog of incentives that could be used to encourage proposals for NAMs in conjunction with existing in-vivo test methods.
- Reviewing current requirements for the consideration of NAMs, and how those might be modified/expanded upon to foster additional consideration by stakeholders.

1. Barriers to implementing NAM's?
2. Suggestions to overcome those barriers?
3. Areas to use NAMs that are currently unavailable?
4. Areas where NAMs are used but are inappropriate?
5. Funding opportunities to research/validate NAMs?
6. Does your group consider or employ the use of NAMs?
7. Methods to prescreen drug or substance candidates for development? Examples?
8. Thoughts on the availability of NAMs (in Academia, Pharma, etc.)?
9. Thoughts on the current state of NAMs in toxicology testing?
10. Examples of successful use of an alternative approach?
11. Suggestions on communication efforts that would promote the use of NAMs?

Ecotoxicity Testing

- ICCVAM Agency needs manuscript
  - Identifies ecotoxicological test data requirements as they relate to agency/ departmental registration and regulation of chemicals and their use
  - Identifies ecotoxicological research and monitoring activities as they relate to agency/departmental mission and programmatic goals
  - Identifies 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 being finalized for publication
  - Characterize the identified methods
  - Determine criteria that are important to regulatory agencies when considering replacement methods for acute fish toxicity



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ELSEVIER

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 [f], 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]

[a] Integrated Laboratory Systems, LLC, P.O. Box 13501, Research Triangle Park, NC, 27709, USA
[b] U.S. Army Engineer Research and Development Center, 3909 Halls Ferry Rd., Vicksburg, MS, 39180, USA
[c] U.S. Environmental Protection Agency, Office of Pesticide Programs, MC7507P, 1200 Pennsylvania Avenue NW, Washington, DC, 20460, USA
[d] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Avenue, Silver Spring, MD, 20993, USA
[e] U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, 7401M, 1200 Pennsylvania Avenue NW, Washington, DC, 20460, USA
[f] U.S. Department of Agriculture, Forest Service, 1400 Independence Ave. SW, Washington, DC, 20250, USA
[g] U.S. Geological Survey, Eastern Ecological Science Center, 12100 Beech Forest Rd, Laurel, MD, 20708, USA
[h] U.S. Department of Agriculture, Wildlife Services National Wildlife Research Center, 4101 LaPorte Ave. Fort Collins, CO, 80521, USA
[i] U.S. Food and Drug Administration, Center for Veterinary Medicine, HFV-161, 7500 Standish Place, Rockville, MD, 20855, USA
[j] National Institute of Environmental Health Sciences, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, P.O. Box 12233, Research Triangle Park, NC, 27709, USA
[k] U.S. Environmental Protection Agency, Office of Research and Development, 8101R, 6201 Congdon Blvd., Duluth, MN, 55804, USA
[l] U.S. Geological Survey, Columbia Environmental Research Center (CERC), Columbia, MO, 65201, USA
[m] U.S. Department of Commerce, National Institute of Standards and Technology, 100 Bureau Drive, Gaithersburg, MD, 2009, USA
[n] U.S. Geological Survey, Eastern Ecological Science Center, 10300 Baltimore Ave, BARC-EAST Bldg 308, Beltsville, MD, 20705, USA
[o] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, 5001 Campus Drive, HFS-009, College Park, MD, 20740, USA
[p] U.S. Department of Agriculture, Animal Care, 4700 River Rd., Riverdale, MD 20737, USA

In Vitro to In Vivo Extrapolation

toxics
MDPI

Review

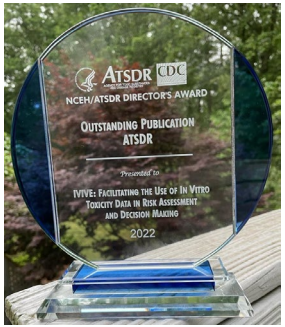
IVIVE: Facilitating the Use of *In Vitro* Toxicity Data in Risk Assessment and Decision Making

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

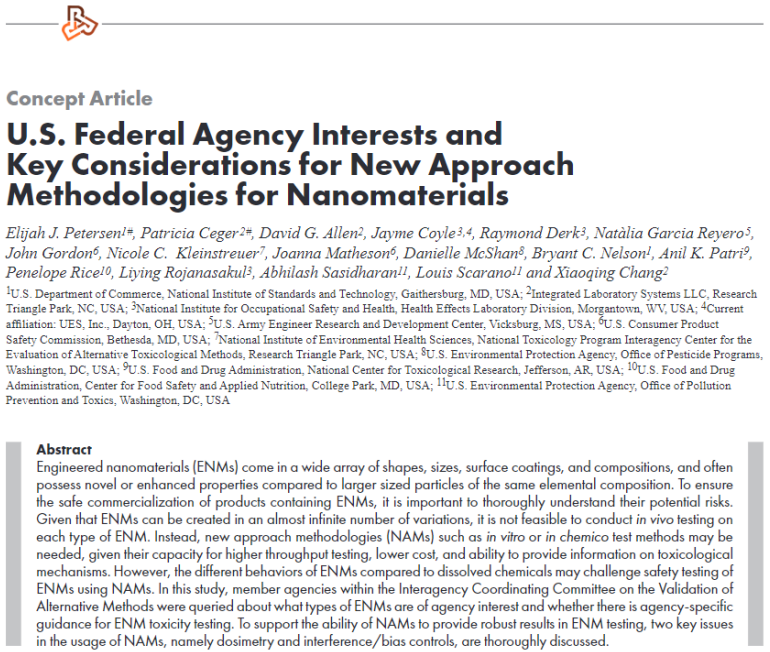
Recognized by Toxics as an "Annual Recommended Review" for 2022 and by ATSDR as the "2022 Outstanding Publication"

- Catalog of current IVIVE methods, models, and case studies; catalog open source and commercially available IVIVE models and software tools
- Describes specific risk assessment purposes that can be achieved with the currently available approaches, and identify gaps; Identify case studies to demonstrate utility and applicability of IVIVE to the needs of risk assessors. (Included in manuscript)



Nanomaterials Testing

- Identify agency requirements and needs for nanomaterial toxicology testing
- Identify other Federal and International efforts in this area
- 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
- ***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

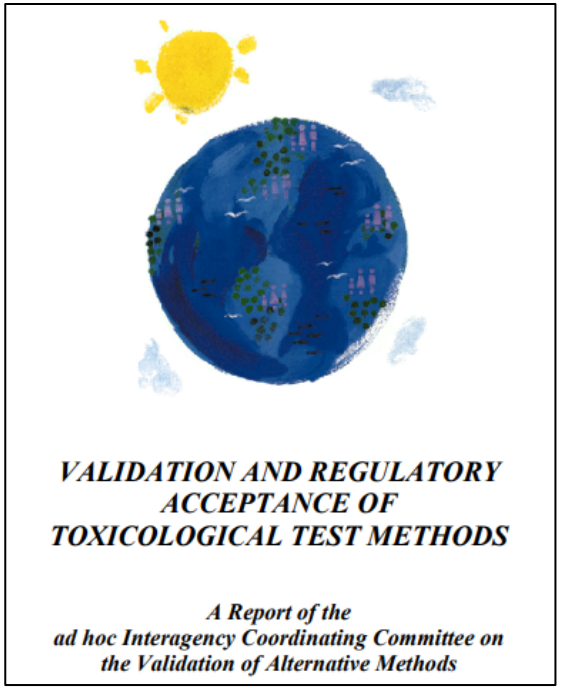
Abstract

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.

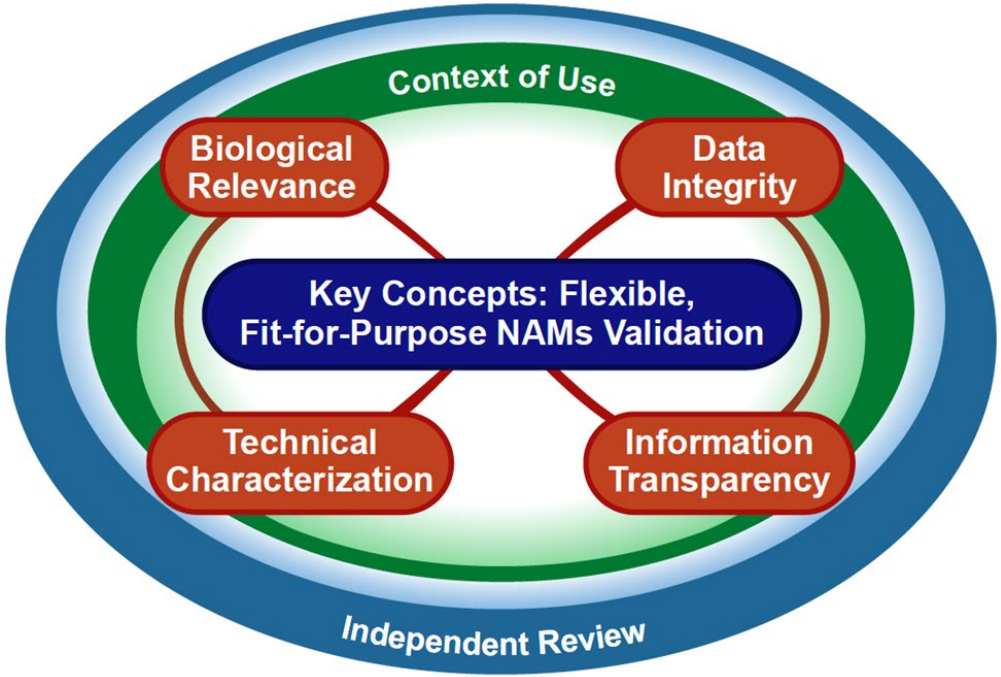
ALTEX 39(2):183-206. https://doi.org/10.14573/altex.2105041.

ICCVAM Validation Workgroup: Updating Guidance for Establishing Confidence

- Updates need to the original document published in 1997
- Underlying principles from OECD 34 remain the same in this new Guidance.
- Introduce the “context of use” terminology
- New guidance will emphasize that validation process should be flexible and adaptable.
- Emphasize the need for communication because regulatory needs may vary across the federal agencies



Updated Guidance for Establishing Confidence: Guiding Principles

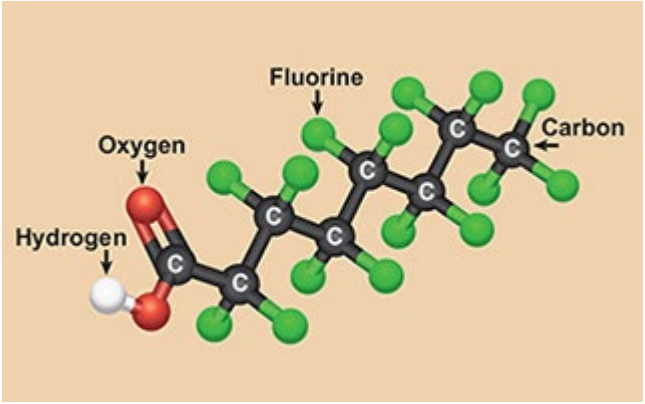


Adapted from van der Zalm et al. (2022).

- Draft document is currently in each agency's clearance process
- Public commenting period to be opened once clearance has completed

New Workgroup: PFAS Testing and Assessment

- Sponsoring agencies: DoD, EPA, FDA
- Workgroup focus: Application of NAMs to evaluating PFAS toxicity
  - NAMs are not being applied to testing PFAS very broadly yet
- Workgroup scope and charge is under development



https://www.niehs.nih.gov/health/topics/agents/pfc/index.cfm

https://www.health.ny.gov/environmental/chemicals/chemicals_and_health/

Questions?

https://ntp.niehs.nih.gov/go/iccvam