Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM Workgroup Updates

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ICCVAM Public Forum
May 20-21, 2024

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
  - Validation
  - PFAS

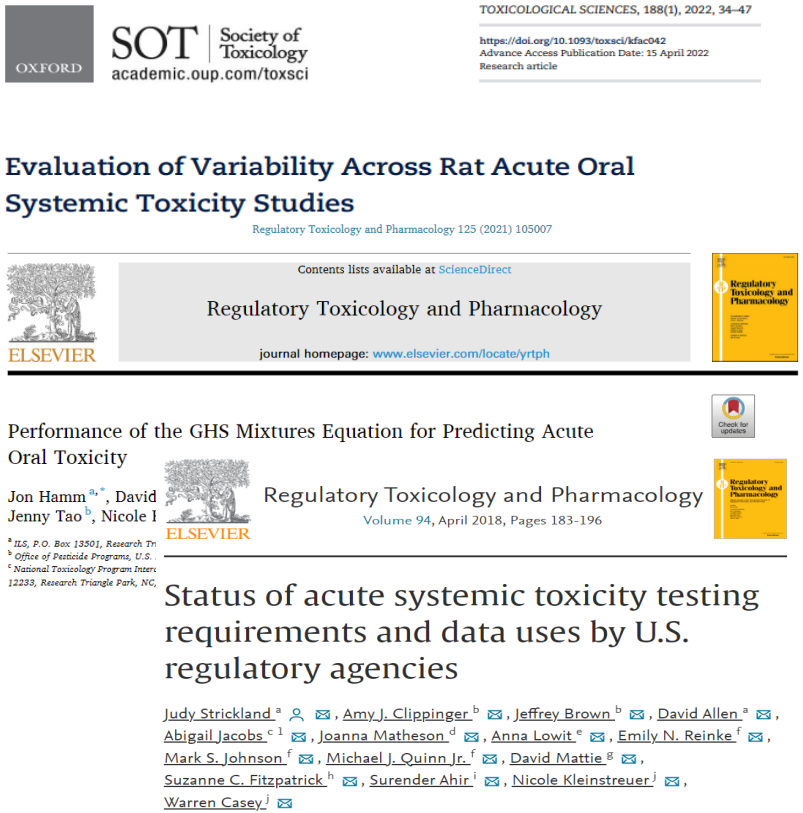
Acute Toxicity Testing

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 published (Strickland et al., 2023; https://doi.org/10.1080/10408444.2023.2240852)

Ongoing - inhalation toxicity

- LC50 database finalized, available on Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/)
- Collaborative modeling project for predicting LC50 launched March 2024


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

Regulatory Toxicology and Pharmacology 125 (2021) 105007
Contents lists available at ScienceDirect
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph
ELSEVIER

Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

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Jenny Tao [b], Nicole I

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12233, Research Triangle Park, NC,

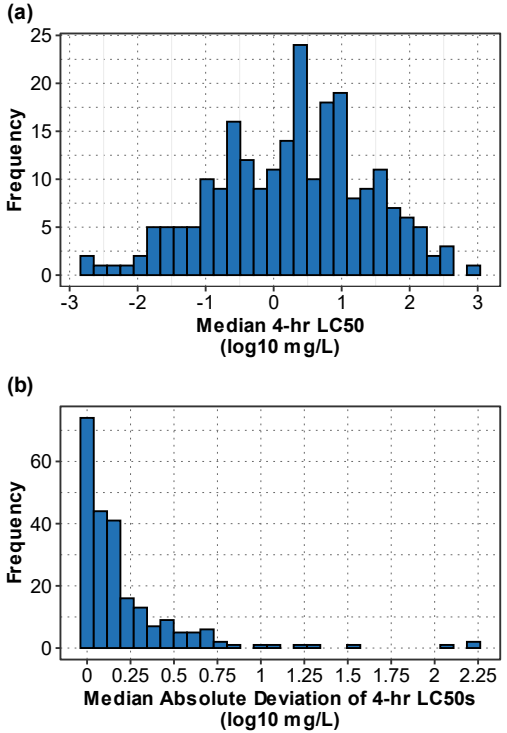
Regulatory Toxicology and Pharmacology
Volume 94, April 2018, Pages 183-196
ELSEVIER

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

Judy Strickland [a], Amy J. Clippinger [b], Jeffrey Brown [b], David Allen [a], Abigail Jacobs [c 1], Joanna Matheson [d], Anna Lowit [e], Emily N. Reinke [f], Mark S. Johnson [f], Michael J. Quinn Jr. [f], David Mattie [g], Suzanne C. Fitzpatrick [h], Surender Ahir [i], Nicole Kleinstreuer [j], Warren Casey [j]

Acute Inhalation Modeling Project

- Collaborative effort to build a modeling approach that predicts acute inhalation toxicity
  - Multi-sector collaboration launched March 2024
  - Define, develop, and execute an appropriate approach for predicting an LC50
  - Dataset is relatively small (approximately 760 chemicals)



Consideration of Alternative Methods

Workgroup Scope

- Work 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.
- Review current requirements for the consideration of NAMs, and how those might be modified/expanded upon to foster additional consideration by stakeholders.

Workgroup Charges

1. Work with stakeholders to publish a white paper on approaches to the use of NAMs.
2. Foster collaborations with authorities outside of the U.S. to share ideas and progress to promote greater harmonization for considering NAMs.
3. Refer the community to available grants devoted to the development of alternatives to live animal use.
4. Identify and improve communication efforts and opportunities that help promote the use of NAMs.
5. Encourage agencies to promote avenues where NAMs can be better considered and leveraged.

Consideration of Alternative Methods

Accomplishments and Next Steps:

- Stakeholder discussions were held between May 2022 and May 2023 with CAMWG members and stakeholder group representatives from agrochemical, industrial chemical, consumer products, pharmaceutical companies, academic researchers, and academic IACUC members.
- The goal was to hear from stakeholders within the toxicology testing community on their experience with the use of NAMs and other alternative methods.
- A white paper is currently being drafted from these discussions and the plan is to publish in ALTEX.
  - Catalogs stakeholder perspectives on various aspects of using NAMs including availability, validity, barriers, and funding opportunities to better understand how more serious consideration and utility of NAMs can be fostered.
  - Covers how alternatives to traditional animal tests are considered in the development of their respective organization's toxicology testing programs.

Ecotoxicity Testing

- 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
  - Characterize the identified methods
  - Determine criteria that are important to regulatory agencies when considering replacement methods for acute fish toxicity
  - Agency input collected on the use of the acute fish toxicity test and NAMs:
    - What does your agency do with acute fish toxicity data?
    - What is your flexibility to use NAMs?
    - What should the data submitter know about your agency's process?
    - Are there legal or regulatory impediments to the adoption of NAMs, for example, are live animal data specifically called for in your agency's regulations?
  - Reference literature is being updated
    - Collecting and extracting manuscripts that employ the acute fish toxicity test and the Fish Embryo Test (OECD TG236) or the Fish Cell Line Acute Toxicity - The RTgill-W1 cell line assay (OECD TG249)

In Vitro to In Vivo Extrapolation

toxics
MDPI

Review

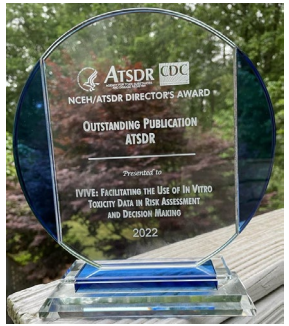
IVIVE: Facilitating the Use of *In Vitro* Toxicity Data in Risk Assessment and Decision Making

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"

- Conduct literature searches for current IVIVE methods, models, and case studies; catalog open source and commercially available IVIVE models and software tools
- Identify ongoing IVIVE efforts and key data needs across different agencies to highlight the different decision contexts of interest
- Determine 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.
- ***Workgroup charges completed - converted to an Expert Group***



Validation Workgroup

Published March 2024
doi: 10.22427/NICEATM-2

- The VWG re-wrote the 1997 report, “Validation and Regulatory Acceptance of Toxicological Test Methods.”
  - Underlying principles from OECD 34 remain the same in the new report.
  - Introduces the “context of use” terminology.
  - Emphasizes that validation process should be flexible and adaptable.
  - Emphasizes the need for communication because regulatory needs may vary across the federal agencies.

- Key concepts of flexible, fit-for-purpose NAMs validation
- Applying the key concepts to build confidence
  - Context of use
  - Biological relevance
  - Technical characterization
  - Data integrity
  - Information transparency
  - Independent review
- U.S. Federal agency acceptance
  - Understanding regulatory needs & decision contexts
  - Context of use considerations
  - Evolution of confidence based on experience gained
- U.S. & international harmonization
- Communication & training to encourage use
- Implementation

Method Developers Forum (MDF)

- A proactive effort to highlight and implement the recommendations detailed within the VWG report and provide an opportunity for NAMs developers to interact with stakeholders around regulatory issues.
- Anticipate holding approximately 2 MDFs per year.
- Each iteration will focus on a specific endpoint/toxicity.
  - First MDF will focus on carcinogenicity (~July 2024).
  - ICCVAM agency and industry stakeholders summarize their information needs for carcinogenicity and potential contexts of use for NAMs.

U.S. Federal Agencies
- Consumer Product Safety Commission (CPSC)
- Environmental Protection Agency (EPA)
  - Office of Pesticide Programs (OPP) Health Effects Division
  - Office of Pollution Prevention and Toxics (OPPT) New Chemicals Division
- Food and Drug Administration (FDA)
  - Center for Food Safety and Applied Nutrition
  - Center for Drug Evaluation and Research
- National Cancer Institute (NCI)
- National Institute for Occupational Safety and Health (NIOSH)
- Occupational Safety and Health Administration (OSHA)

Agrochemicals
- Syngenta

Pharmaceuticals
- TBD

  - Developers demonstrate how their methods address the topic of interest and consider the key concepts from the VWG report in a webinar.
- Future topics include developmental toxicity, reproductive toxicity, cardiovascular toxicity, neurotoxicity, systemic toxicity, specific target organ toxicity (e.g., liver).

PFAS Testing and Assessment

- Sponsoring agencies: DoD, EPA, FDA
- Current efforts
  - Assess the current state of the science for PFAS and NAMs
    - The WG is drafting a state of science White Paper on NAMs for PFAS, including a review of available information for PFAS testing using NAMs and overarching challenges/ data gaps for application of NAMs for regulatory assessment.
- Future
  - Conduct a workshop/conference session on the application of NAMs for specific PFAS
  - Report the outcome of the workshop/session and future directions

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

Questions?

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