Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM Workgroup Update

ICCVAM Public Forum

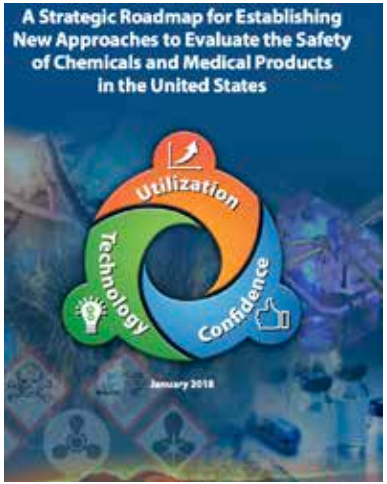
May 27, 2021

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

ICCVAM Workgroups

- ICCVAM establishes ad hoc workgroups to perform specific tasks important for the development or validation of alternatives to animal testing. The workgroups are composed of representatives from agencies that use or require data from the topic of interest.

- Workgroups play a key role in carrying out ICCVAM activities, including implementing the goals of the ICCVAM Strategic Roadmap



Connect end users with the developers of alternative methods

Establish new validation approaches that are more flexible and efficient

Ensure adoption and use of new methods by both regulators and industry

ICCVAM Workgroups

- Draft a scoping document to identify U.S. agency requirements and decision contexts for toxicity testing data
- Coordinate efforts with stakeholders
- Identify, acquire, and curate high quality data from reference test methods and other relevant sources
- Identify and evaluate new approach methodologies (NAMs)
- Facilitate regulatory acceptance of NAMs

Current ICCVAM Workgroups

- Acute Toxicity Workgroup
- Ecotoxicology Workgroup
- In Vitro to In Vivo Extrapolation Workgroup
- Nanomaterials Workgroup
- Read Across Workgroup
- Validation Workgroup
- ICCVAM Expert Groups

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

ICCVAM Expert Groups

ICCVAM also establishes expert groups to facilitate communication among agencies on a specific area of interest. Expert groups can be established from workgroups that have completed their charge tasks, or by agency representatives that share interest in a topic for which no specific activity has been identified. ICCVAM currently has expert groups in the areas of developmental and reproductive toxicity, developmental immunotoxicity, FAIR data standards, metrics, microphysiological systems, ocular and dermal irritation, and skin sensitization.

Acute Toxicity Workgroup (ATWG) Charges

ICCVAM Sponsor Agencies: EPA, DoD

- 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)

ATWG Roster

- Xinrong Chen (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Donald Cronce (DoD, Co-chair)
- Natalia Garcia-Reyero (DoD)
- Jeffery Gearhart (DoD)
- Tyler Goralski (DoD)
- Matthew Grogg (DoD)
- David Mattie (DoD)
- Akeisha Owens(DoD)
- Heather Pangburn (DoD)
- Brian Pate (DoD)
- Emily Reinke (DoD)
- Marc Williams (DoD)
- Aiguo Wu (DoD)
- Ryan Vierling (DOT)
- Anna Lowit (EPA, OPP)
- Grace Patlewicz (EPA, ORD, Co-chair)
- Elissa Reaves (EPA, OPP)
- Jenny Tao (EPA, OPP)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Deana Holmes (OSHA)

ICATM Liaison Members

- Pilar Prieto Peraita (EURL ECVAM)

NICEATM Support Staff (ILS)

- Judy Strickland
- Agnes Karmaus
- David Allen

Ecotoxicity Workgroup (EcoWG) Charges

ICCVAM Sponsor Agencies: DOI, EPA

- Identify ecotoxicological test data requirements as they relate to agency/ departmental registration and regulation of chemicals and their use (Manuscript in progress)
- Identify ecotoxicological research and monitoring activities as they relate to agency/departmental mission and programmatic goals (Same as above)
- Identify endpoints needed by each federal agency and commonalities and differences between agencies (Same as above)
- 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 (Same as above)
- Determine criteria that are important to regulatory agencies when considering replacement methods for acute fish toxicity (Same as above)

Timeline for manuscript completion: Agency Needs for Ecotoxicity Testing

Milestone	Date
Compile 3rd draft at WG member request - circulate to WG	30-Apr-21
Workgroup meeting to discuss draft	19-May-21
Deliver final draft to ICCVAM agencies for review and clearance	11-Jun-21
Manuscript submitted to journal	NLT 23-Jul-21
Journal review comments received	Depends on journal
Revised manuscript submitted to journal	1 month after comments received
Journal acceptance	Depends on journal
Galley proof received	Depends on journal
Galley corrections submitted	2 weeks after proofs are received

Timeline for manuscript completion: Prioritizing Alternatives for Acute Fish Toxicity

Milestone	Date
Complete Collection of Agency Responses	1-Jan-20
Determine who in the workgroup will be primary agency POCs (assuming different from previous MS)	1-Jan-20
Circulate MS outline to workgroup for comments	30-Apr-20
Compile first draft MS - circulate to workgroup	NLT – 1-Jun-21
Workgroup meeting to discuss draft	TBD
Compile second draft - circulate to workgroup	TBD
Workgroup meeting to discuss draft	TBD
Deliver final draft to ICCVAM agencies for review and clearance	TBD
Manuscript submitted to journal	TBD
Journal review comments received	Depends on journal
Revised manuscript submitted to journal	1 month after comments received
Journal acceptance	Depends on journal
Galley proof received	Depends on journal

EcoWG Roster – May 2021

- Kristina M. Adams (USDA)
- Carol Clarke (USDA)
- Katherine Horak (USDA)
- Patrice Klein (USDA)
- Jim Warren (USDA)
- Natalia Garcia-Reyero (DOD)
- Kurt A. Gust (DOD)
- Edward Perkins (DOD)
- Emily N. Reinke (DOD)
- Marc Williams (DOD)
- Paula F. P. Henry (DOI)
- Jessica K. Leet (DOI)
- Barnett A Rattner (DOI)
- William Eckel (EPA/OPP)
- Douglas Harwood (EPA/OPP)
- Michael Lowit (EPA/OPP)
- Scott Lynn (EPA/OPP)
- Jennifer Brennan (EPA/OPPT)
- Karen Eisenreich (EPA/OPPT)
- Kellie Fay (EPA/OPPT)
- Kara Koehrn (EPA/OPPT)
- Carlie Lalone (EPA/ORD)
- Teresa Norberg-King (EPA/ORD)
- Michael Elias (EPA/OW)
- Laura Phillips (EPA/OW)
- Amy Bergdale (EPA/Region 3)
- Debra Denton (EPA/Region 9)
- Raanan Bloom (FDA, CDER)
- James Laurenson (FDA, CDER)
- Sarah Winfield (FDA, CFSAN)
- Hoshing Chang (FDA, CTP)
- Wesley Hunter (FDA, CVM)
- Nicole Kleinstreuer (NIEHS)
- Elijah Petersen (NIST)

NICEATM Support Staff (ILS)

- Patricia Ceger
- Jon Hamm
- David Allen

In Vitro to In Vivo Extrapolation Workgroup (IVIVE-WG) Charges

ICCVAM Sponsor Agencies: ATSDR, EPA

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

Current IVIVE-WG Deliverables

Timeline for completion of Manuscript

Milestone	Date
Complete questionnaire on regulatory needs of IVIVE approaches	Complete
Circulate MS outline to workgroup for comments	Complete
IVIVE controlled vocabulary	Complete
Identify case studies to demonstrate utility of IVIVE to the needs of risk assessors	Complete
Have workgroup meeting to discuss section writer and begin writing	Complete
Compile initial draft MS - circulate to workgroup for content review	Complete
Compile first draft MS - circulate to workgroup	June 2021
Workgroup meeting to discuss draft	June 2021
Compile revised draft - circulate to workgroup	July 2021
Workgroup meeting to discuss revised draft	August 2021
Final draft manuscript to agency authors for clearance	September 2021
Manuscript submitted to journal	Depends on agency clearances (NLT 3 months)
Transition to an expert group	TBD after manuscript publication

IVIVE-WG Roster

- Moiz Mumtaz (ATSDR, co-chair)
- Michael Babich (CPSC)
- John Gordon (CPSC)
- Eric Hooker (CPSC)
- Joanna Matheson (CPSC)
- William Eck (DOD)
- Christy Foran (DOD)
- Natalia Garcia-Reyero (DOD)
- Jeffrey Gearhart (DOD)
- Heather Pangburn (DOD)
- Lisa Sweeney (DOD)
- Chris Brinkerhoff (EPA, OCSPP)
- Daniel Chang (EPA, OCSPP)
- Martin Phillips (EPA, OCSPP)
- Anna Lowit (EPA, OPP)
- Cecilia Tan (EPA, OPP, co-chair)
- John Wambaugh (EPA, ORD)
- Barbara Wetmore (EPA, ORD)
- Paul Brown (FDA, CDER)
- Alexandre Ribeiro (FDA, CDER)
- Ronald Wange (FDA, CDER)
- Suzanne Fitzpatrick (FDA, CFSAN)
- Brenna Flannery (FDA, CFSAN)
- Shruti Kabadi (FDA, CFSAN)
- Annie Lumen (FDA, NCTR)
- Tracy Chen (FDA, OCS)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Elijah Petersen (NIST)
- Pertti (Bert) Hakkinen (NLM)

ICATM Liaison Members

- Alicia Paini (EURL ECVAM)
- Yuji Ishii (JaCVAM)
- Fumiaki Shono (JaCVAM)

NICEATM Support Staff (ILS)

- Xiaoqing Chang
- Lauren Browning
- Patricia Ceger
- David Allen

Nanomaterials Workgroup (NanoWG) Charges

ICCVAM Sponsor Agencies: CPSC, NIST

- Identify agency requirements and needs for nanomaterial toxicology testing (Requirements collated; Manuscript submitted to ALTEX)
- Identify other Federal and International efforts in this area (Same as above)
- Work with ICATM partners to identify international regulatory requirements for nanomaterial toxicity testing (Same as above)
- 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 (Same as above)

Current NanoWG Deliverables

Timeline for completion of Manuscript

Milestone	Date
Complete Collection of Agency Responses	Complete
Circulate MS outline to workgroup for comments	Complete
Survey on dosimetry characterization in *in vitro* testing	Complete
Identify case studies for dosimetry characterization	Complete
Feedback and revision from workgroup members on the control measurements	Complete
Workgroup meeting to discuss section and begin writing	Complete
Compile first draft MS - circulate to workgroup	Complete
Workgroup meeting to discuss draft	Complete
Compile revised draft - circulate to workgroup	Complete
Document returned from WG prior to submission for agency clearance	Complete
Final draft manuscript to agency authors for clearance	Complete
Manuscript submitted to journal	May 2021
Transition to an expert group	TBD after manuscript publication

NanoWG Roster

- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Natalia Garcia-Reyero (DOD)
- Alan Kennedy (DOD)
- Laura Stolle (DOD)
- Danielle McShan (EPA, OPP)
- Abhilash Sasidharan (EPA, OPPT)
- Katherine Tyner (FDA, CDER)
- Rakhi M. Dalal-Panguluri (FDA, CDRH)
- Peter Goering (FDA, CDRH)
- Penelope Rice (FDA, CFSAN)
- Anil Patri (FDA, NCTR)
- Jayme Coyle (NIOSH, HELD)
- Raymond Derk (NIOSH, HELD)
- Liying Rojanasakul (NIOSH, HELD)
- Warren Casey (NIEHS)
- William Gwinn (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Srikanth Nadadur (NIEHS)
- Nigel Walker (NIEHS)
- Bryant Nelson (NIST)
- Elijah Petersen (NIST, chair)
- Vytas Reipa (NIST)

NICEATM Support Staff (ILS)

- Xiaoqing Chang
- Patricia Ceger
- David Allen

ICCVAM Read Across Workgroup (RAWG) Charges

ICCVAM Sponsor Agencies: CPSC, NIST

- 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. (in progress)
- 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)

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

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[c] Center for Devices and Radiological Health, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD, 20993, USA
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[e] Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD, 20740, USA
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[g] U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD, 20850, USA
[h] National Library of Medicine, 6707 Democracy Blvd., Bethesda, MD, 20892, USA
[i] Agency for Toxic Substances and Disease Registry, 1600 Clifton Rd., Chamblee, GA, 30341, USA
[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

Recent ICCVAM Read Across WG Meetings

Milestone	Description	Date
March 2019 Teleconference	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	March 26, 2020
May 2020 Teleconference	Case Study Submitted by "**EPA Revisiting and updating chemical groupings with new approach methodologies"** Dan Chang	May 29, 2020
July 2020 (A) Teleconference	Review of work group scope and charge and case studies presented.	July 13, 2020
July 2020 (B) Teleconference	Discussion on future options for work group and if/when to transition to expert group.	July 15, 2020
October 2020 Teleconference	Presentation from CPSC: Draft Plan **"Assessing the Risks of Organohalogen Flame Retardants (OFRs): A Class Approach"** Mike Babich	October 30, 2020

RAWG Roster

- Moiz Mumtaz (ATSDR)
- Patricia Ruiz (ATSDR)
- Michael (Mike) Babich (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Natalia Garcia-Reyero (DOD)
- Louis (Gino) Scarano (EPA/OPPT)
- Todd Stedeford (EPA/OPPT)
- Lucina Lizarraga (EPA/ORD)
- Grace Patlewicz (EPA/ORD – chair)
- Diego Rua (FDA/CDRH)
- Suzanne Fitzpatrick (FDA/CFSAN)
- Brenna Flannery (FDA/CFSAN)
- Patra Volarath (FDA/CFSAN)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Pertti (Bert) Hakkinen (NLM)

ICATM Liaisons

- Takashi Yamada (JaCVAM)

NICEATM Support Staff (ILS)

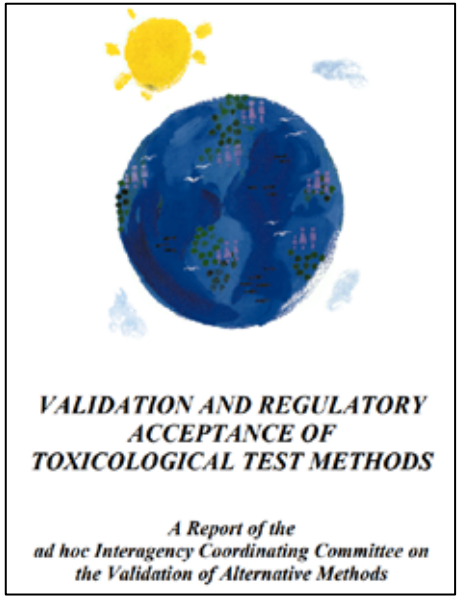
- John Rooney
- Neepa Choksi
- Amber Daniel
- Agnes Karmaus
- David Allen

ICCVAM Validation Workgroup (VWG) Charges

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.
- To be accompanied by implementation plans



Recent ICCVAM VWG Meetings

Milestone	Description	Date
ICCVAM Strategy Meeting	ICCVAM membership agreed that the level of effort, resources, and administrative support required to revise the ICCVAM guidance document warranted officially forming the Validation Workgroup (VWG). Members for the VWG were nominated.	05 March 2021
Workgroup Teleconference	Workgroup members discussed and finalized the scope & charges.	05 May 2021
Co-chairs Teleconference	Co-chairs and select workgroup members that volunteered to contribute to the initial draft discussed the draft outline of the new ICCVAM guidance document.	17 May 2021
Workgroup Teleconference	Discussion of draft outline with the VWG membership.	TBD (June 2021)

VWG Roster

- Moiz Mumtaz (ATSDR)
- John Gordon (CPSC, co-chair)
- Donald Cronce (DOD)
- Natalia Garcia-Reyero (DOD)
- Matthew Johnson (DOD)
- Emily Reinke (DOD)
- George Lathrop, Jr. (VA ORD)
- Anna Lowit (EPA/OPP)
- Scott Lynn (EPA/OPP)
- Monique Perron (EPA/OPP)
- Stephanie Padilla (EPA/ORD)
- Nisha Sipes (EPA/ORD)
- Paul Brown (FDA/CDER)
- Jennifer Goode (FDA/CDRH)
- Suzanne Fitzpatrick (FDA/CFSAN, co-chair)
- Anneliese Striz (FDA/CFSAN)
- Connie Kang (FDA/CTP)
- Tracy Chen (FDA/OCS)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Elijah Petersen (NIST, co-chair)
- Janet Carter (OSHA)

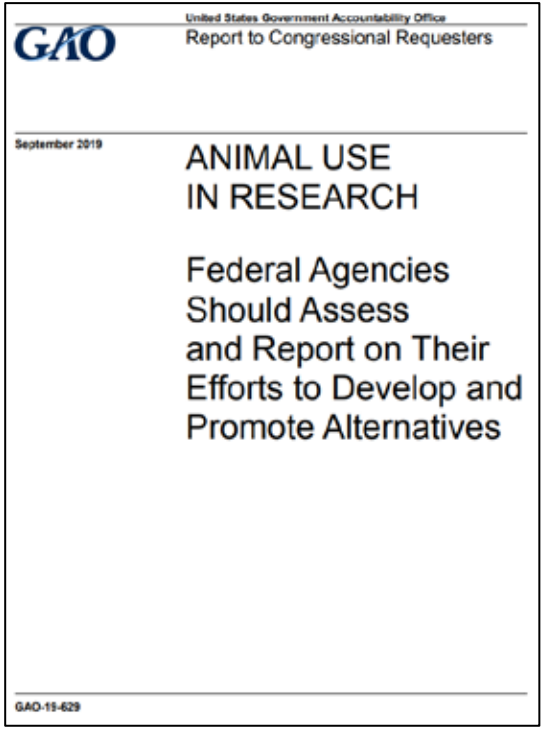
NICEATM Support Staff (ILS)

- Agnes Karmaus
- Amber Daniel
- David Allen

Metrics Workgroup

- In response to a request by Congress, the U.S. Government Accountability Office (GAO) investigated and reported on how federal agencies ensure that alternative methods are being considered and used.
- GAO recommended to Congress that federal agencies establish a workgroup through ICCVAM to propose metrics for assessing progress on the development and promotion of alternative methods.

"the Director of the NIH's National Institute of Environmental Health Sciences should (1) facilitate the establishment or designation of a workgroup of representatives of the Interagency Coordinating Committee on the Validation of Alternative Methods member agencies to ***develop metrics that the agencies could use to assess the progress they have individually or collectively made toward reducing, refining, or replacing animal use in testing*** *and (2) incorporate those metrics into the committee's biennial progress reports."*



United States Government Accountability Office

GAO

Report to Congressional Requesters

September 2019

ANIMAL USE IN RESEARCH

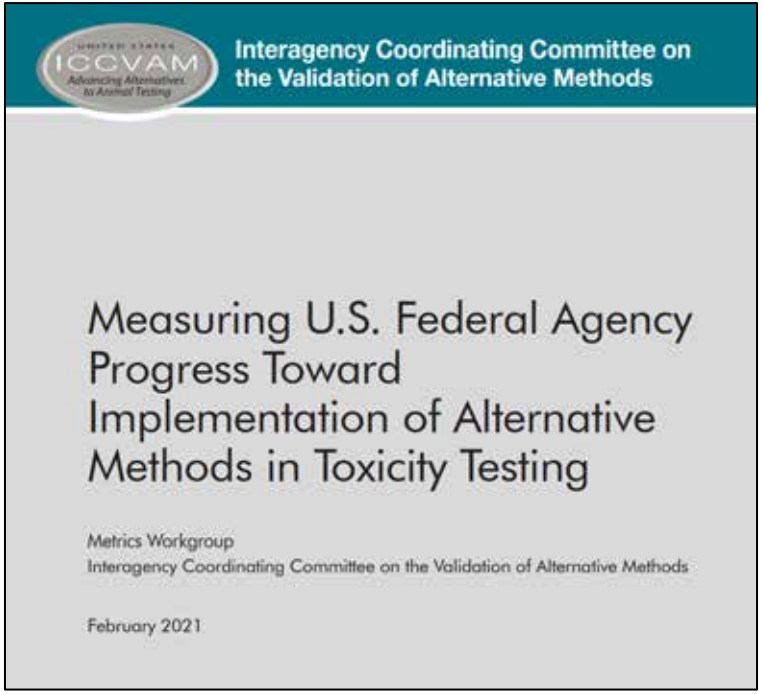
Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives

GAO-19-629

Metrics ~~Workgroup~~ Expert Group

- In response, ICCVAM established its Metrics Workgroup in early 2020.
- The workgroup included members from nine ICCVAM agencies.
- Workgroup charge: Determine how agencies can best address the GAO report's recommendations within the context of the ICCVAM Authorization Act.
- **Document published in February 2021**

The ICCVAM Metrics Workgroup found that no one set of metrics can be used by all ICCVAM member agencies. The workgroup instead recommends that each agency develop its own metrics that are relevant and practical to their unique situation. This document describes the recommendations of the ICCVAM Metrics Workgroup along with references and other materials that can be used to follow federal agency progress in promoting the use of alternative toxicological methods.



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