



Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM Update

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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
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 Library of Medicine • Occupational Safety and Health Administration

Priority Areas of Focus

- Acute systemic toxicity
- Skin sensitization
- Endocrine disruptors
- Biologics (to be presented by FDA)
- Communications
- International coordination & participation

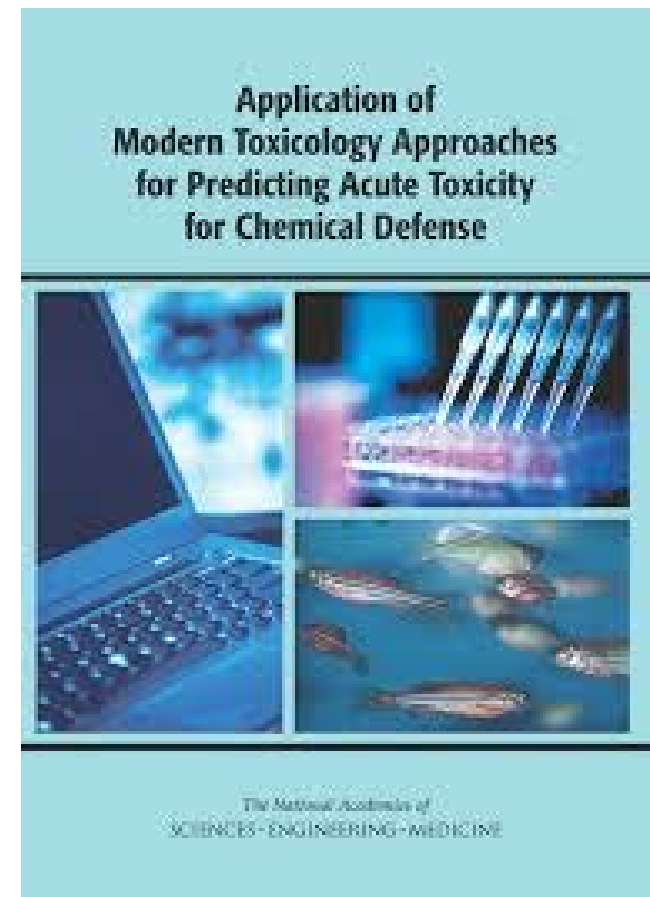
ICCVAM Acute Toxicity Working Group

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
- Evaluate *in vitro* and *in silico* approaches for predicting acute oral, dermal and/or inhalation systemic toxicity
- Evaluate the usefulness of the GHS additivity formulas for classifying formulations and mixtures for acute systemic toxicity tests
- Contribute to a scoping document that outlines the current requirements and testing needs for U.S. and international regulatory authorities
- Develop a draft ICCVAM strategy and roadmap on using *in vitro* and *in silico* approaches to replace, reduce, and refine animal use in acute systemic toxicity testing

Longer Term: Strategy to Reduce and Replace Animal Use for Acute Toxicity

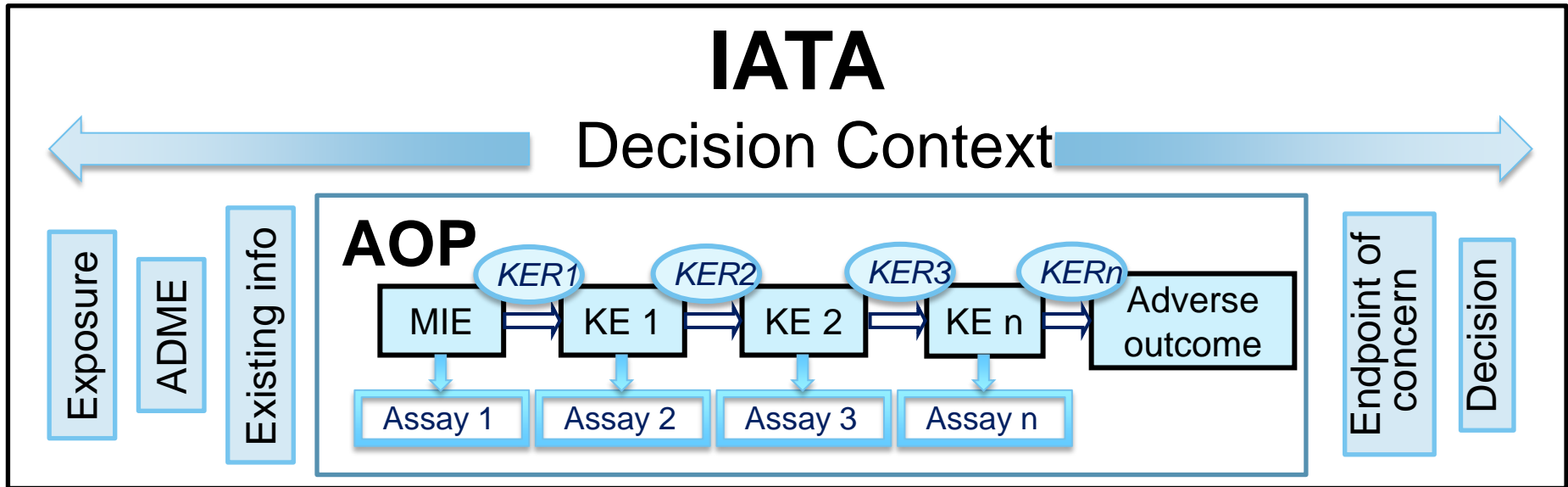
- Build from the conceptual framework outlined in the NRC DoD report
- Tiered prioritization strategy for using databases, assays, models, and tools to predict acute toxicity
 - Balances the need for accuracy and timeliness



ICCVAM Skin Sensitization Working Group

- Goal: Develop integrated approaches to testing and assessment (IATA) for skin sensitization
- Building models to predict skin sensitization hazard for LLNA (mouse), humans, and potency
 - Physicochemical properties
 - An *in silico* method (read-across using OECD QSAR Toolbox)
 - The three *in chemico* or *in vitro* assays validated by EURL ECVAM
 - Direct peptide reactivity assay (DPRA), KeratinoSens, and the human cell line activation test (h-CLAT)

Integrated Approach to Testing and Assessment (IATA): OECD Working Definition



“a structured approach that strategically integrates and weights all relevant data to inform regulatory decisions regarding potential hazard and/or risk and/or the need for further targeted testing and therefore optimizing and potentially reducing the number of tests that need to be conducted.”

ICCVAM Skin Sensitization Models

- Prediction of hazard – LLNA (yes/no)
 - h-CLAT, *in silico* prediction, and 6 physicochemical properties
 - Accuracy = 96%, Sensitivity = 95%, Specificity = 100%
 - KeratinoSens + Toolbox + DPRA + 6 physicochemical properties
 - Accuracy = 89%, Sensitivity = 84%, Specificity = 100%
 - KeratinoSens + h-CLAT + Toolbox + 6 physicochemical properties
 - Accuracy = 89%, Sensitivity = 90%, Specificity = 86%
- Submitted as a case study to OECD

Research article

Journal of
Applied Toxicology

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Integrated decision strategies for skin sensitization hazard

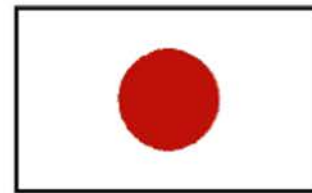
Judy Strickland^a, Qingda Zang^a, Nicole Kleinstreuer^a, Michael Paris^a, David M. Lehmann^b, Neepta Choksi^a, Joanna Matheson^c, Abigail Jacobs^d, Anna Lowit^e, David Allen^a and Warren Casey^{f*}

ICCVAM Skin Sensitization Models

- Prediction of hazard – human (yes/no)
 - Best model uses DPRA, h-CLAT, KeratinoSens, *in silico* prediction, log P
 - Accuracy = 92%, Sensitivity = 93%, Specificity = 89%
- Prediction of hazard – human & LLNA (potency, 3 categories)
 - Uses DPRA, h-CLAT, KeratinoSens and 6 physicochemical properties
 - LLNA – accuracy = 92% for the test set of 26 substances
 - Human – accuracy = 88% for the test set of 24 substances (physicochemical properties not important)
- Publications:
 - Strickland et al. 2016. Multivariate Models for Prediction of Human Skin Sensitization Hazard
 - Accepted with revision by Journal of Applied Toxicology
 - Zang et al. (Draft In Preparation). Prediction of Skin Sensitization Potency Using Machine Learning Approaches

International Cooperation on Alternative Test Methods (ICATM)

- First ever ICATM Workshop on the international regulatory applicability and acceptance of alternative non-animal approaches to skin sensitization assessment of chemicals used in a variety of sectors



ICATM Workshop on Skin Sensitization

- October 4-5, 2016; hosted by EURL-ECVAM, Ispra, Italy
 - Facilitate a common understanding of the available non-animal approaches
 - Identify the current regulatory requirements for skin sensitization in different regions that could be satisfied with non-animal approaches
 - Define a set of performance based criteria for regulatory use of defined approaches
 - Identify obstacles to regulatory acceptance of alternative approaches and strategies to resolve them
 - Issue recommendations for specific regulatory applications in defined chemical sectors

ICATM Workshop on Skin Sensitization

- October 4-5, 2016; hosted by EURL-ECVAM, Ispra, Italy
- Currently collecting additional data to expand current datasets
 - Paired in vitro & LLNA data that could be used to assess various IATAs
 - Data provided by July, 2016 will be compiled

ICCVAM Reference Chemicals Working Group

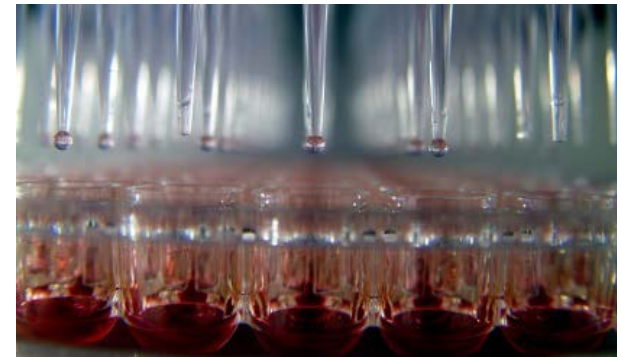
- Representatives from ICCVAM member agencies, ICATM partners (EURL-ECVAM, JaCVAM, KoCVAM, and Health Canada)
 - ER reference chemicals, agonist (Uterotrophic and *in vitro*)
 - Metabolism
 - AR reference chemicals, agonist & antagonist (Hershberger and *in vitro*)
- Scope has been expanded to include chemical effects on thyroid hormone and steroidogenesis

ICCVAM Communications

- Communities of Practice webinar in January, 2016
 - Fundamentals of Using Quantitative Structure-Activity Relationship Models and Read-across Techniques in Predictive Toxicology
 - Alex Tropsha, Ph.D., University of North Carolina at Chapel Hill
 - Louis Scarano, Ph.D., Office of Pollution Prevention and Toxics, U.S. EPA
- ICCVAM Public Forum – expanded for 2016 to maximize time for agency updates and stakeholder discussion
- 3Rs Strategy and Roadmap, SACATM Discussion on September 27-28, 2016
- Included stakeholder presentations/discussion during ICCVAM working group meetings

ICCVAM Biennial Progress Report 2014-2015

- Comprehensive summary of member agency activities relevant to the ICCVAM mission in 2014-2015
- Text complete, document is currently in production
- Will be published as a web document in July 2016
- <http://ntp.niehs.nih.gov/go/iccvam-bien>



ICCVAM VMT and Peer Review Participation

- JaCVAM: Eye Irritation Test Methods
 - Vitrigel-EIT; LabCyte Cornea Model; SIRC-CVS validation studies complete
 - Jill Merrill (FDA-CDER) served on the VMT
 - Bert Hakkinen (NLM) invited to serve on the peer review panel
- JaCVAM: Multi-ImmunoTox Assay (MITA, immunotoxicity testing)
 - Dori Germolec (NIEHS) VMT member
- JaCVAM: Amino acid Derivative Reactivity Assay (ADRA)
 - Skin sensitization test; mechanistically similar to DPRA, but reportedly has an expanded applicability domain relative to DPRA
 - Grace Patlewicz (EPA-NCCT) recommended for the VMT
- JaCVAM: Hand1-Luc Embryonic Stem Cell Test (Hand1 Luc EST)
 - Designed to detect potential embryotoxicants; validation study complete
 - Tom Knudsen (EPA-NCCT) recommended for the peer review
- EURL ECVAM: ESAC Working Group: Skin sensitization
 - Peer review of the LuSens and U-SENS test methods
 - Joanna Matheson (CPSC)



NIST is Joining ICCVAM!

- Will be the first agency added since ICCVAM Authorization Act of 2000

NIST

**National Institute of
Standards and Technology**

U.S. Department of Commerce

Questions?