UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

Interagency Coordinating Committee on the Validation of Alternative Methods

Fostering the Use of Efficient, Flexible, and Robust Practices to Establish Confidence in New Methods

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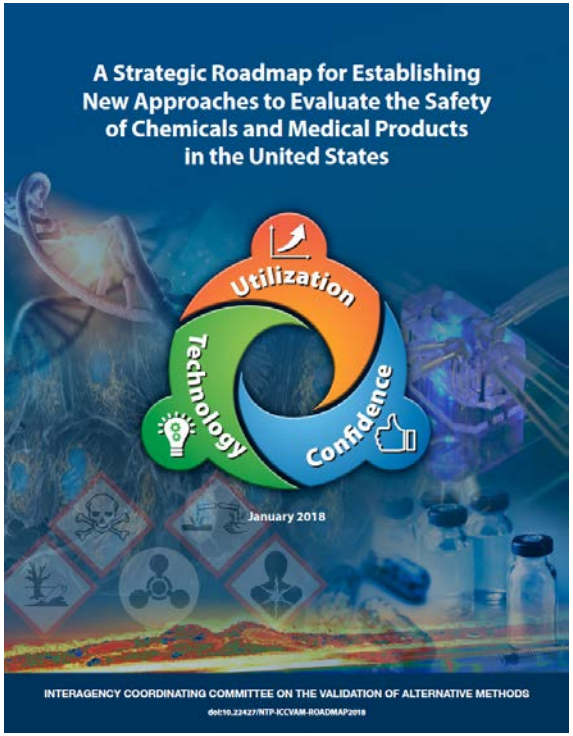
US Army Public Health Command

SACATM Meeting
September 5, 2018

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 Institute • National Institute of Standards and Technology • Occupational Safety and Health Administration

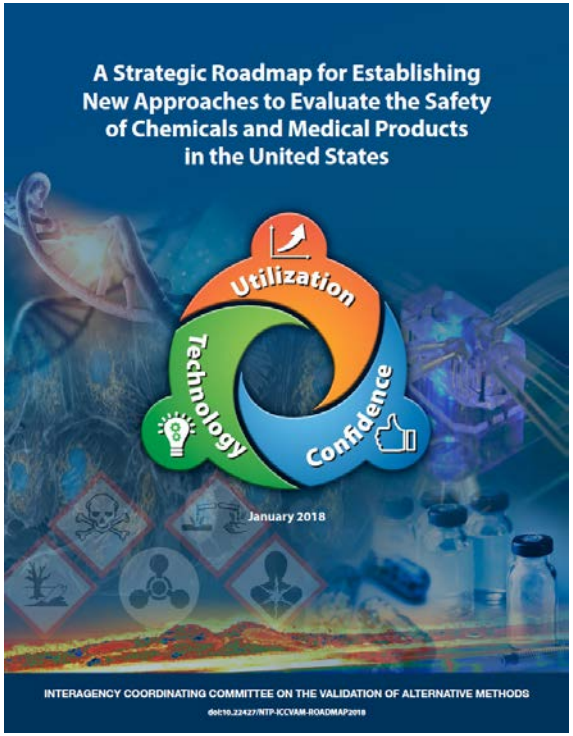
Keys to Implementation

- Clearly delineate testing requirements and context of use
- Promote the use of new approaches for establishing confidence
- Utilize public-private partnerships to promote cross-sector communication and cooperation



Keys to Implementation

- Clearly delineate testing requirements and context of use
  - Failure to consider the ultimate context of use is one of the most frequently cited reasons for lack of agency and industry adoption of NAMs.
  - Agencies must clearly communicate their needs and all possible contexts for both the existing animal study and NAM.
- Promote the use of new approaches for establishing confidence
- Utilize public-private partnerships to promote cross-sector communication and cooperation



Testing Requirements/Agency Needs

Regulatory Toxicology and Pharmacology 94 (2018) 183–196
Contents lists available at ScienceDirect
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph

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]

Toxicology in Vitro 48 (2018) 53–70
Contents lists available at ScienceDirect
Toxicology in Vitro
journal homepage: www.elsevier.com/locate/toxinvit

Alternative approaches for acute inhalation toxicity testing to address global regulatory and non-regulatory data requirements: An international workshop report

Amy J. Clippinger[a,*], David Allen[b], Annie M. Jarabek[c], Marco Corvaro[d], Marianna Gaça[e], Sean Gehen[f], Jon A. Hotchkiss[g], Grace Patlewicz[h], Jodie Melbourne[a], Paul Hinderliter[i], Miyoung Yoon[j], Dongeun Huh[k], Anna Lowit[l], Barbara Buckley[c], Michael Bartels[m], Kelly BéruBé[n], Daniel M. Wilson[g], Ian Indans[o], Mathieu Vinken[p]

Regulatory Toxicology and Pharmacology 95 (2018) 52–65
Contents lists available at ScienceDirect
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph

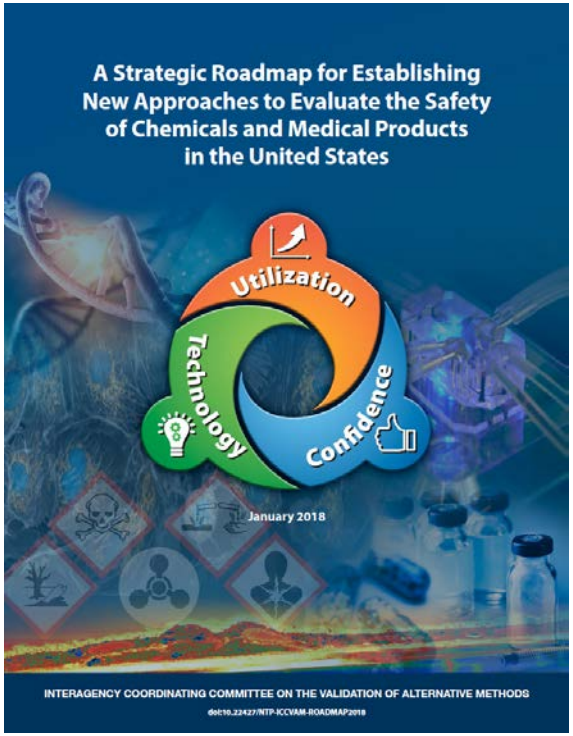
International regulatory requirements for skin sensitization testing

Amber B. Daniel[a], Judy Strickland[a,*], David Allen[a], Silvia Casati[b], Valérie Zuang[b], João Barroso[b], Maurice Whelan[b], M.J. Régimbald-Krnel[c], Hajime Kojima[d], Akiyoshi Nishikawa[d], Hye-Kyung Park[e], Jong Kwon Lee[e], Tae Sung Kim[e], Isabella Delgado[f], Ludmila Rios[g], Ying Yang[h], Gangli Wang[i], Nicole Kleinstreuer[j]

- Each paper identifies requirements, needs, and decision contexts
- US regulatory requirements for skin sensitization paper (*Strickland et al.*) submitted to Archives of Toxicology
- US regulatory requirements for eye irritation paper (Choksi et al.) submitted to Cutaneous and Ocular Toxicology

Keys to Implementation

- Clearly delineate testing requirements and context of use
- Promote the use of new approaches for establishing confidence
  - Investigate approaches driven by human biology, exposure, and mechanistic relevance and don't rely on animal data as the reference for evaluating performance
  - Establish forums to discuss best approaches to expedite regulatory acceptance of methods already in use for in-house screening by industry
  - Provide agency and stakeholder case studies illustrating how alternative approaches have successfully been evaluated or implemented
- Utilize public-private partnerships to promote cross-sector communication and cooperation



Skin Sensitization Alternatives: Expanding Substance Space Coverage

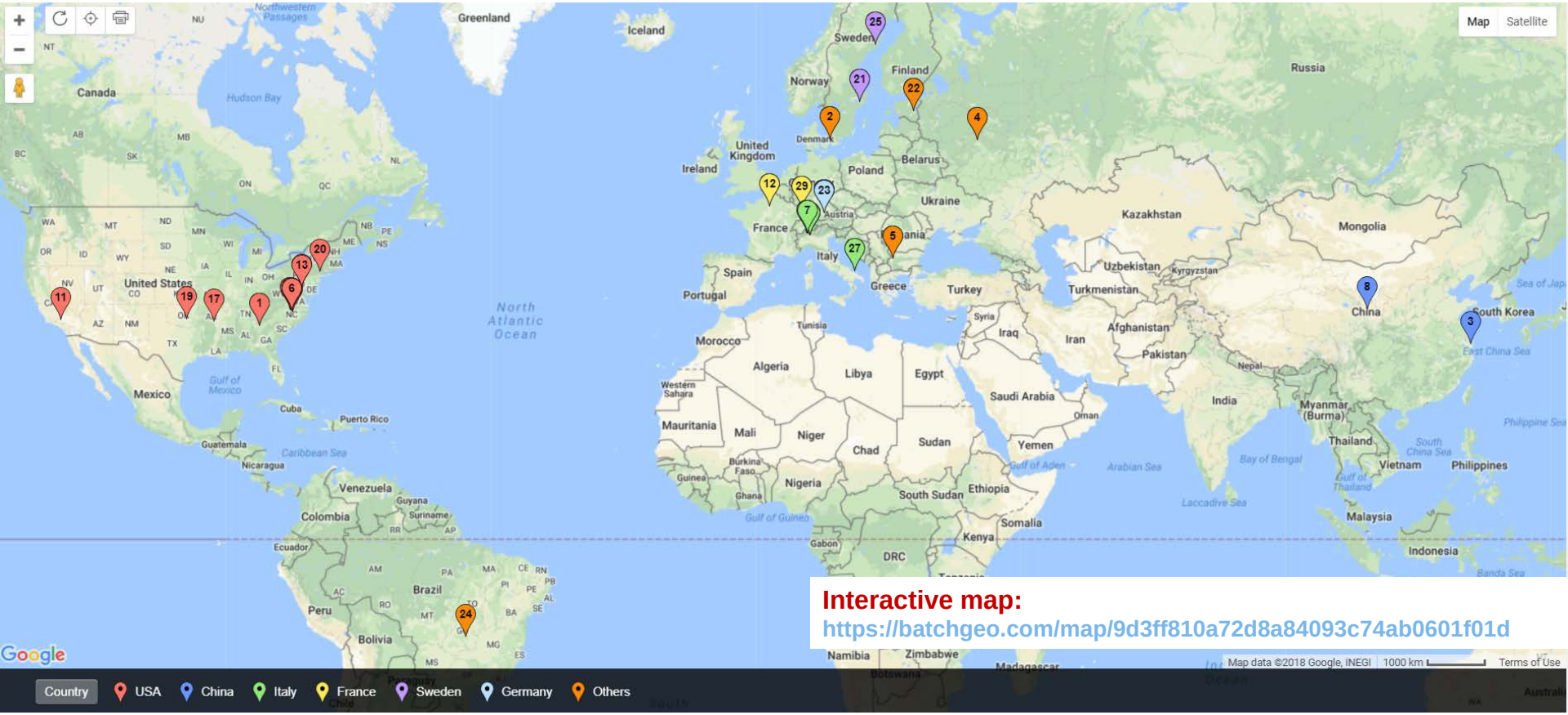
- NTP (*Tox Branch*/*D. Germolec*) is testing additional substances in three alternative test methods:
  - DPRA, KeratinoSens, hCLAT
- Expanded substance space includes:
  - pesticide/agrochemical formulations, dermal excipients, personal care product products, “challenge” chemicals *in vivo* LLNA and human data
- Compiled nominations from multiple ICCVAM agencies/partners (n=266)
  - EPA: OPP, OPPT, ORD
  - Consumer Product Safety Commission
  - Food and Drug Administration
  - National Toxicology Program
  - ICATM partners
- Testing began in late 2017 (n=135)
- Coordinating with Corteva to test formulations already assessed in DPRA and KeratinoSens™ in the hCLAT assay

Workshop on Predictive Models for Acute Oral Systemic Toxicity

- International QSAR modeling groups tasked with building models to predict acute oral systemic toxicity
- Model outputs (quantitative and categorical) based on agency input - coordinated by ICCVAM ATWG
- 32 groups from the US, Europe, and Asia responded with 135 models for LD50, EPA and GHS categories, and binary nontoxic vs all others and very toxic vs all others.
- Models were qualitatively and quantitatively assessed and combined into consensus models.
- Attendees in-person: 89; webcast: 215
- Workshop summary manuscript accepted by Computational Toxicology

https://ntp.niehs.nih.gov/go/tox-models

Modeling Participants Locations



Consensus Models: Applicability to ICCVAM Agencies

- Requesting chemicals from ICCVAM agencies and regulated industry stakeholders to evaluate the performance of the consensus models for acute oral toxicity.
- Available in vivo or in vitro data for each substance
  - Will allow to assess how useful the models are for the types of chemicals regulated by each agency/center
  - Approximately 9,000 substances identified

Prospective Eye Irritation Testing of Agrochemical Formulations

- Eye Methods to be evaluated: BCOP, ICE, Neutral red release, EpiOcular (time to toxicity and TG 492 protocols), PorCORA (to evaluate reversibility of effects)
- Phase 1: small number (n=6) tested in all assays to demonstrate proof-of-concept (COMPLETE)
- Phase 2: comprehensive assessment of applicability with a larger set (n=40)
  - Phase 2A (n=10): All methods included
  - Phase 2B (n=30): Define methods to be included after Phase 2A
- Coded formulations donated by companies: BASF, Bayer, Dow-DuPont (Corteva Agrisciences), Monsanto, Syngenta
- Co-organized by NICEATM and PISC, with VMT members from ICCVAM and ODIWG, EURL ECVAM, PMRA, and industry

Study Logistics

Testing Laboratories

- Institute for In Vitro Sciences
  - NRR and BCOP
- CiTox Labs
  - ICE
- Mattek Corporation
  - EO
- MB Research Laboratories
  - PorCORA

Chemical Distribution

- National Toxicology Program
  - Formulations donated by AgChem companies
  - Coded substances to be sent to testing labs
  - Additional material may be archived at NTP for future use

Skin Irritation: Private-Public Partnership

- Optimization of 3D skin model for testing antimicrobial cleaning products (AMCPs)
- Companies donated AMCPs
- Optimization/testing ongoing at IIVS
- Also collecting data and potential reference agrochemical formulations from companies for testing (PISC and NICEATM coordinating)

Global Skin Sensitization Project

- Objective: analysis of available non-animal defined approaches (DAs)
- Collaboration with Cosmetics Europe
  - Curation/generation of
    - *in vivo* LLNA and human data
    - *in vitro* cell-based data that maps to AOP
    - *in silico* computer predictions, chemical structural features & properties
- Qualitative and quantitative evaluation of OECD-submitted DAs
- Fully transparent approach (i.e., build open-source code packages)
- Evaluate performance against LLNA and human hazard/potency categories

Hoffmann et al. 2018 Crit Rev Tox
Kleinstreuer et al. 2018 Crit Rev Tox

Non-Animal Approach Evaluation

Most non-animal testing strategies evaluated so far perform **better** than the LLNA at predicting human skin sensitization hazard and potency.

(And when compared to the LLNA, are equivalent in performance to the LLNA at predicting itself.)

Hoffmann et al. 2018 Crit Rev Tox
Kleinstreuer et al. 2018 Crit Rev Tox

Newly formed ICCVAM Workgroup Charges

- ICCVAM Read Across Workgroup
  - *Identify case studies that demonstrate utility of read-across analyses in a regulatory setting and identify key data needs for regulatory acceptance.*
  - *Summarize best practices that are focused on the application and implementation of read-across for the different regulatory settings of interest.*

- ICCVAM IVIVE Workgroup
  - *Identify case studies to demonstrate utility and applicability of IVIVE to the needs of risk assessors*
  - *Determine best practices for IVIVE analyses and approaches/models/tools to implement them.*

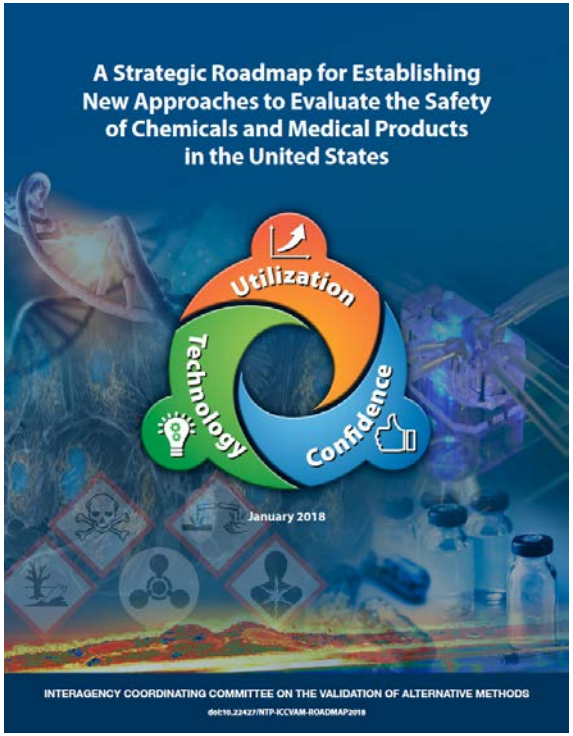
Newly formed ICCVAM Workgroup Charges

- ICCVAM DART Workgroup
  - *Establish a stakeholder group comprised of both government and nongovernment scientists to coordinate efforts towards developing and implementing integrated new approach methodologies for developmental toxicity testing.*

- ICCVAM Ecotoxicology Workgroup
  - *Establish a stakeholder group comprised of both government and nongovernment scientists to coordinate efforts towards developing and implementing alternative approaches for ecotoxicity testing.*

Keys to Implementation

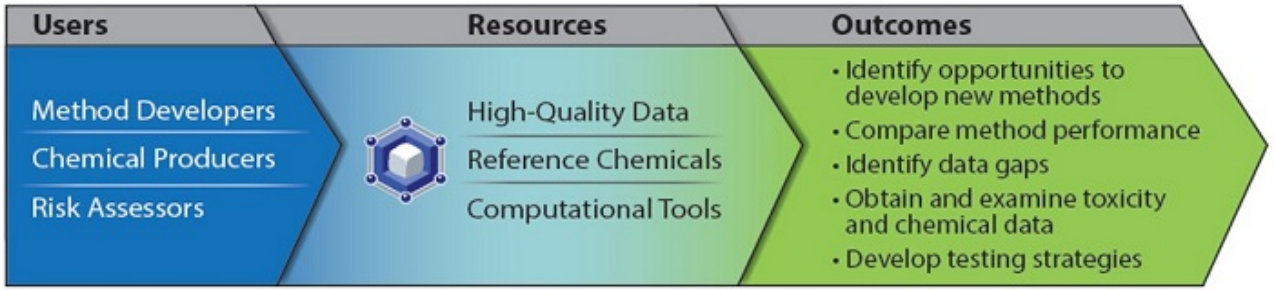
- Clearly delineate testing requirements and context of use
- Promote the use of new approaches for establishing confidence
- Utilize public-private partnerships to promote cross-sector communication and cooperation
  - Identify and collate sources of high-quality human toxicological and exposure data
  - Create centralized data access points that are publicly available and easily accessible
  - Actively solicit the submission and collation of parallel data from animal studies and alternative method



Data Collection

- Multiple conventional & antimicrobial registrants have kindly provided data to support our “six-pack” efforts
- We continue to collect additional, voluntary data submissions to expand current datasets
  - Paired *in vitro* & in vivo data that could increase coverage of various defined approaches
  - Replicate in vivo studies to help assess variability
- NICEATM and PISC sent letters of request to industry consortia

Integrated Chemical Environment (ICE)



- **ICE provides free online access to:** https://ice.ntp.niehs.nih.gov/
  - Curated in vivo and in vitro chemical test data
  - In silico toxicity predictions and chemical property data
  - Reference chemical lists
  - Computational tools and workflows related to safety testing
- **ICE supports:**
  - Data integration: brings together available data, including data on formulations
  - Results exploration: dynamic, graphical exploration with publication-quality graphics
  - Data analysis: online workflows allowing characterization of data

Stakeholder Meetings

- NICEATM and PISC Stakeholder WebEx meetings
  - PISC and NICEATM WebEx meetings with industry partners
  - Provides data templates and details regarding inclusion in ICE
  - Agrochemical, chemical, and personal care products companies
- Regular EPA stakeholder teleconferences to discuss updates, data needs, etc.
  - NICEATM, PISC, PCRM, Industry

Discussion Questions

- What is the most appropriate mechanisms for validating and establishing confidence in NAMs? How should the existing ICCVAM validation guidelines be updated to be more appropriate for validation of NAMs? How do we best integrate with international efforts?
- What types of public-private partnerships are needed to help establish confidence in NAMs?
- What are the most relevant comparators for NAMs?
- What is the single most important action that federal agencies could take to establish confidence in NAMs?
- What is the single most important action that regulated industry should take to establish confidence in NAMs?
- *Lead Discussants: Coleman, Milchak, Gehen*