Interagency Coordinating Committee on the Validation of Alternative Methods

Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session 1: ICCVAM – Past, Present, Future
Wednesday, September 2, 2020

➢ 20 Years of Scientific Accomplishments

Presenter: Dr. Emily Reinke, U.S. Department of Defense

This presentation commemorates the 20th anniversary of the ICCVAM Authorization Act by reviewing key milestones and accomplishments of the committee over the last two decades.

Background

- PL 106-545: ICCVAM Authorization Act of 2000

➢ Implementing the Strategic Roadmap

Presenter: Dr. Nicole Kleinstreuer, NIEHS/NICEATM

Following the publication in early 2018 of "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States", ICCVAM and NICEATM have focused their efforts on several targeted roadmap implementation plans for specific toxicity endpoints. These plans are intended to facilitate achieving the goals of the roadmap, specifically to connect end users with the developers of new approach methodologies (NAMs), foster the use of efficient, flexible, and robust practices to establish confidence in new methods, and ensure adoption and use of new methods by both federal agencies and regulated industry. This presentation will outline the stepwise activities that have been undertaken for various acute toxicity endpoints to define testing needs and decision contexts, identify available tests and computer models, develop integrated approaches to testing and assessment, and address both scientific and non-scientific challenges. These activities have been coordinated via ICCVAM workgroups and in collaboration with industry and NGO partners. Examples of successful regulatory and industry stakeholder implementation of NAMs and outstanding issues to address will be discussed, with an eye towards further development of implementation plans for additional, more complex, endpoints.

Background

- A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States
- Implementation plans developed for acute endpoints:
    - Acute systemic toxicity
      Details at https://ntp.niehs.nih.gov/go/roadmap-acutetox
    - Skin and eye irritation
      Details at https://ntp.niehs.nih.gov/go/roadmap-irrit

- Skin sensitization
  Details at https://ntp.niehs.nih.gov/go/roadmap-sensit

➢ NTP Approaches to Assessment of Dermal Hypersensitivity: Using Alternative Methods to Predict Skin Sensitization

Presenter: Dr. Dori Germolec, NIEHS/DNTP

To date, there has been a great deal of progress in using in vitro models to assess chemical sensitization, and in particular, dermal hypersensitivity and irritancy. In 2013, the OECD published an adverse outcome pathway (AOP) for skin sensitization linking molecular initiating events and cellular and tissue effects in the sensitization process to specific adverse outcomes.

For skin sensitization, these key events include: 1) covalent interaction with skin proteins, 2) activation of inflammatory cytokines and induction of cytoprotective genes, 3) induction of inflammatory cytokine and surface molecules and mobilization of dendritic cells, and 4) activation of T cells. Several in vitro testing methods for assessment of hypersensitivity have been validated in international interlaboratory ring trials, and combinations of these methods (so-called “defined approaches”) have been shown to provide superior performance to the existing animal tests when compared to human data. It is clear from these efforts that while no individual in vitro test can recapitulate the hypersensitivity response in its entirety, integrated strategies using varying combinations of in vitro, in chemico, and/or in silico methods could be highly accurate in identifying potential skin sensitizers.

To further investigate the utility of these approaches, NICEATM solicited chemical nominations from ICCVAM federal agencies for which there were existing local lymph node assay data but only limited in vitro evaluation. Through the NTP Immunotoxicology contract with Burleson Research Technologies, chemicals were screened using the KeratinoSens® assay, the direct peptide reactivity assay, and the human cell line activation test (h-CLAT). Just under 200 chemicals and chemical formulations have been tested to date and analysis of the data is ongoing. The list of chemicals includes pesticides, formulations, excipients and industrial agents. A subset of this data has already been used by the U.S. Environmental Protection Agency in their “Draft Human Health and Ecological Risk Assessments for Several Pesticides for Several Isothiazolinones”, which was published in the *Federal Register* in May. This is the first use of such information in regulatory risk assessment and marks a major milestone in the use of alternative methods, as defined approaches have been demonstrated to be more reliable and human relevant than the commonly employed in vivo test methods.

Background:

- Non-animal Methods to Predict Skin Sensitization (II): An Assessment of Defined Approaches
- Hazard Characterization of Isothiazolinones in Support of FIFRA Registration Review

➢ Measuring Success of 3R Initiatives

Presenter: Dr. Suzanne Fitzpatrick, U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition

ICCVAM’s 2018 strategic roadmap called for it to identify appropriate metrics for monitoring progress and measuring success in adopting alternatives. Facilitating the establishment of such a workgroup would help the committee and its member agencies better monitor their progress across the range of their efforts to reduce animal use and report members’ progress to the public. In response to a report issued by the U.S. Government Accountability Office, ICCVAM has formed an ICCVAM Metric Committee with senior representatives from the different federal agencies.

This committee is chaired by the U.S. Food and Drug Administration and the U.S. Department of Defense. Progress towards developing a White Paper for tracking 3Rs success will be discussed.

Background:

- EPA New Approach Methods Workplan
- FDA's Predictive Toxicology Roadmap
- ICCVAM Biennial Progress Report

➢ The Strategic Roadmap: What Lies on the Horizon?

Presenter: Dr. Warren Casey, NIEHS/NICEATM

The successful implementation of the ICCVAM Strategic Roadmap requires a continuous cycle of connecting end users with developers of NAMS, establishing confidence in the new approaches and facilitating their adoption by industry stakeholders and federal agencies. Horizon scanning must therefore be continuously conducted to identify technologies, innovations, and trends with the potential to feed into the Roadmap cycle as well as those with the potential to disrupt it. Doing so will help ICCVAM develop strategies and prioritize activities to help ensure the effective implementation of contemporary advances in science and technology. This talk will highlight notable scientific and technological advances that will be critical to future ICCVAM efforts, update SACATM on critical technologies previously discussed with the committee, and highlight areas of concern with the potential to disrupt future advances. SACATM members will be asked to comment on the perceived relevance of these areas and identify other areas that ICCVAM should consider.

Background:

- Balancing Machine Learning and Mechanistic Modeling
- New Approach Methodologies for Exposure from EPA's ExpoCast Project
- Advancing Regulatory Science by Innovation: In Vitro Microphysiological Systems
- Beyond 3-D Models: Building Confidence in Microphysiological Models
- Anticipated Science and Technology – Microphysiological Systems
- Moving Beyond Animal Data as the Gold Standard
- Biomedical Data Translator