



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

Federal Collaboration

- In 2000, Congress passed the ICCVAM Authorization Act and established Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
 - Comprised of 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information.
- NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) of the NIEHS provides scientific and operational support for ICCVAM technical evaluations and related activities.

Background

- ICCVAM and NICEATM work together to promote the development, validation, and regulatory acceptance of new and revised regulatory test methods and integrated testing and decision strategies that replace, reduce, and refine the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.
- In 2013, Director of NIEHS and ICCVAM announced that ICCVAM and NICEATM will be making significant changes to the focus and priorities of both organizations (<http://iccvam.niehs.nih.gov/announcements/ICCVAM-all/2013-02-06-EHP.htm>).

Introduction & Outline of the Presentation

- The 2013 draft document, “A New Vision and Direction for ICCVAM,” describes the initial steps towards a new strategic direction for ICCVAM and NICEATM.
- Draft covers three areas:
 - ICCVAM priority setting and science focus areas for immediate ICCVAM resource investment
 - Plans to improve communications with stakeholders and the public
 - Warren Casey will cover this topic
 - Exploring new paradigms for the validation and utilization of alternative toxicological methods.

New Vision & Direction for ICCVAM

- ICCVAM priority setting & current science focus areas:
 - Member agencies are taking a more active role in priority setting and operations of the Committee.
 - Change in approach:
 - Streamline the number of active projects where the science has advanced
 - There is a reasonable likelihood of success with a reasonable timeframe (1-5 years) for implementing into regulatory use.
 - Working groups of agency experts established for specific tasks
 - Maintain flexibility to reorient efforts to maximize potential progress towards use of alternative approaches

New Vision & Direction for ICCVAM

- ICCVAM is developing revised procedures for the submission/nomination of new assays or projects.
 - These revised procedures will be provided to the public for comment in the future.
 - Key change to the process, however, will be the need for documented support by at least one federal agency.
 - This federal agency will take the role of ‘sponsor’ for the proposed project, thereby ensuring that work done by ICCVAM is aligned with the needs of the agencies.
- Recently, there have discussions with ECVAM about better international coordination
 - Proposals for collaboration/coordination will be announced as part of SACATM (September, 2014)

ICCVAM Progress on Priorities

- Short-term: Several projects were initially identified
 - Acute oral and dermal toxicity testing
 - Skin sensitization
 - Johanna Matheson (CPSC) will update next
 - Biologics:
 - Leptospira vaccine potency: reduction in hamster usage
 - Acellular Pertussis Vaccines: Alternatives to the Murine Histamine Sensitization Test (HIST)
 - Abby Jacobs (FDA) will update

Reducing Animal Use for Acute Toxicity Assessments

- NICEATM & EPA are collaborating to evaluate the relative contribution of acute and dermal toxicity tests in providing information related to labeling for pesticides
- Acute oral and dermal toxicity testing
 - *Step 1: Compile dataset(s) of oral & dermal LD₅₀ studies*
 - Step 2: Comparison analysis---How do the results of acute and dermal Lethal Dose (LD₅₀) tests compare?
 - Step 3: Implication---Are both the oral & dermal LD₅₀ tests needed for labelling?

Example of OPP's use of Acute Dermal LD₅₀ Data: Pesticide Handlers

- Pesticide handlers are those who mix, load and apply pesticides
- Pesticide labeling requirements describe how protective clothing, respiratory protection and engineering controls are assigned to products based on toxicity of the end use product
- Risk assessment is also used to assign protective equipment to labels in addition to these criteria

Table 1. Handler PPE for WPS Products

| Route of Exposure | Toxicity Category by Route of Exposure of End-Use Product | | | |
|---|---|---|--|-----------------------------------|
| | I DANGER | II WARNING | III CAUTION | IV CAUTION |
| Dermal Toxicity or Skin Irritation Potential ¹ | Coveralls worn over long-sleeved shirt and long pants | Coveralls worn over short-sleeved shirt and short pants | Long-sleeved shirt and long pants | Long-sleeved shirt and long pants |
| | Socks | Socks | Socks | Socks |
| | Chemical-resistant footwear | Chemical-resistant footwear | Shoes | Shoes |
| | Chemical-resistant Gloves ² | Chemical-resistant Gloves ² | Chemical-resistant Gloves ² | No minimum ⁴ |
| Inhalation Toxicity | Respiratory protection device ³ | Respiratory protection device ³ | No minimum ⁴ | No minimum ⁴ |
| Eye Irritation Potential | Protective eyewear ⁵ | Protective eyewear ⁵ | No minimum ⁴ | No minimum ⁴ |

Oral-Dermal Hazard Classification Analyses in the Literature

- Several published studies have investigated comparability between oral and dermal acute hazard classifications to assess whether tests for both routes are needed
 - Creton et al. (2010) reported on 240 pesticide actives and 438 industrial chemicals
 - Seidle et al. (2011) reported on 1569 industrial substances and 337 pesticide actives
 - Moore et al. (2013) reported on 225 substances from the European Chemicals Agency (ECHA) database and 110 pesticide actives from Creton et al. (2010)
- These have focused on technical active ingredients & have not used the EPA-OPP categorization system.

NICEATM Oral-Dermal LD₅₀ Data Evaluations

- In 2012, NICEATM presented a poster at SOT, “Analysis to Determine if Acute Oral Systemic Toxicity Data Can Be Used to Estimate and Avoid Acute Dermal Systemic Toxicity Testing.”
 - This initial analysis concluded that acute oral toxicity data could not be used to determine acute dermal hazard,
 - 346 Substances with rat oral and rabbit dermal data
 - 81 Substances with rat oral and rat dermal data
- In 2013, a re-evaluation was initiated with collaboration from EPA’s Office of Pesticide Programs
 - Reconsider data analysis strategy with limit test data
 - Improved QA/QC of data set
 - Focus on dermal data from rats only for more appropriate comparison to oral rat data

NICEATM Oral-Dermal LD₅₀ Data Evaluations

- From 2013 to now, work continues
 - Studies compiled for both formulations & technical active ingredients.
 - However, the focus of current efforts is on the formulations:
 - Formulation LD₅₀ studies are used for determining PPE for pesticide handlers.
 - Potential animal savings comes primarily from formulation acute studies
 - There are 1000's of end use products registered by EPA
 - The dermal LD₅₀ data for the technical active ingredients are often used in ecological assessments.

Oral-Dermal LD₅₀ Data Evaluation Project

- A draft dataset of acute & dermal LD₅₀ data for formulations is close to completion
 - QA/QC is still on-going
 - Evaluation of ‘chemical-space’ coverage
- Current draft version includes:
 - Conventionals, antimicrobials, biopesticides
 - 12 different formulation types
 - Toxicity (particularly absorption) can be influenced by the nature of the exposure
 - Toxicity categories I, II, III, IV
 - >400 different combinations of active ingredients (single ai’s, multiple ai’s in various combinations)

Oral-Dermal LD₅₀ Data Evaluation Project

- Next Steps:
 - Finish compiling & QA/QC of the dataset
 - NICEAM will be conducting statistical analysis
 - Followed by....
 - Discussions between NICEATM & EPA-OPP on the findings
 - Write up the project for public comment
 - Will include the dataset & the statistical analysis
 - Timeline: Goal is to have the draft analysis & summary for public comment by end of September, 2014

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Biologics: *Leptospira* vaccine potency



- The Animal and Plant Health Inspection Service (APHIS) of the USDA is developing ways to use fewer hamsters in the maintenance of *Leptospira* challenge cultures
- The effects of this change in hamster usage will be monitored over the next 5 years
 - Collect, track, and interpret information regarding hamster usage from annual reports
 - Plan to have an update at the upcoming SACATM meeting (September 16, 2014)



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Communications Plan

- At least 3 opportunities each year for ICCVAM-Stakeholder interactions
 - January: Communities of Practice
 - May: Public Stakeholder Forum
 - September: SACATM Meeting

Exploring New Paradigms

- ICCVAM has identified a long-term goal---to work towards a new definition/concept of “validation” in order to speed up acceptance of methods & to be more responsive to on-going paradigm shifts in toxicity testing.
 - Better alignment with the vision laid out by the National Academy of Sciences in the 2007 NRC Report on Toxicity Testing in the 21st Century (NRC, 2007) while simultaneously fulfilling the mission of ICCVAM to implement the 3Rs of toxicity.
 - Less emphasis on one-to-one replacements
 - Instead, identify predictive, integrated test strategies that combine in silico approaches and multiple in vitro assays
 - Evaluating a variety of statistical approaches to assembling components of a test battery, as well as statistical models for integrating all relevant information and assay results
 - ITS for skin sensitization testing is the first example

Any Questions?