UNITED STATES ICCVAM
Advancing alternatives to animal testing

Interagency Coordinating Committee on the Validation of Alternative Methods

A New Vision and Direction for ICCVAM

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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

Introduction and Outline of the Presentation

- The 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
  - Exploring new paradigms for the validation and utilization of alternative toxicological methods

New Vision and Direction for ICCVAM

- ICCVAM priority setting and 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 to 5 years) for implementing into regulatory use
    - Maintain flexibility to reorient efforts to maximize potential progress towards use of alternative approaches
  - Short-term: Initially three projects were identified
    - Biologics: *Leptospira* vaccine potency
    - Acute oral and dermal toxicity testing
    - Skin sensitization

New Vision and Direction for ICCVAM

- ICCVAM priority setting & current science focus areas (cont'd):
  - 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

Biologics: *Leptospira* vaccine potency

USDA

- The Animal and Plant Health Inspection Service (APHIS) of the USDA is committed to decreasing hamster usage in *Leptospira* vaccine potency testing
- Currently developing a mechanism 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
- A 25% to 30% decrease in animal usage by the industry is anticipated

Skin sensitization

- "*ICCVAM's Proposed Activities on Alternative Skin Sensitization Test Methods and Testing Strategies*"
  - OECD documents on the AOP for skin sensitization
  - Significant worldwide progress in the development of *in vitro* / *in chemico* / *in silico* test batteries which do not use intact animals
  - ICCVAM is developing a strategy for how it plans to evaluate skin sensitization test methods and for making progress towards skin sensitization testing without the use of intact animals

Acute Oral and Dermal LD_{50} Testing

How do the results of acute and dermal Lethal Dose (LD_{50}) tests compare for purposes of providing information related to pesticide hazard labeling and use of personal protective equipment (PPE)?

Guideline	Study Type	Food Use	Non-Food Use
870.1100	Acute oral toxicity - Rat	R	R
870.1200	Acute dermal toxicity - Rat /Rabbit	R	R
870.1300	Acute inhalation toxicity - Rat	R	R
870.2400	Primary eye irritation - Rabbit	R	R
870.2500	Primary dermal irritation - Rabbit	R	R
870.2600	Dermal sensitization - Guinea Pig	R	R
870.6200	Acute neurotoxicity - Rat	R	R

Use of Acute Dermal LD_{50} Data for Pesticide Handler Personal Protective Equipment

- 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]

From Chapter 10, Label Review Manual. http://www.epa.gov/oppfead1/labeling/lrm/chap-10.pdf

Use of Acute Dermal LD_{50} Data for Post-Application Risk Mitigation

- Post-application worker exposure can result from activities like harvesting in previously treated fields
- Risks are managed using an administrative approach (Restricted Entry Interval), REIs are the time for residues to dissipate to appropriate levels. Defined by:
  - Acute toxicity of the active ingredient (end use product data can also be used if other not available)
  - Risk assessment is also used to define REIs
- If based on acute toxicity, REIs are assigned as follows:
  - 48 hours if category 1 (can be 72 hours if an OP and arid area)
  - 24 hours if category 2
  - 12 hours if category 3 or 4

Oral-Dermal Hazard Classification Analyses

- Several published studies 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 using the 4-category UK hazard classification system
  - Seidle et al. (2011) reported on 1569 industrial substances using the 4-category EU Dangerous Substances Directive hazard classification and 337 pesticide actives using a 5-category Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification
  - Moore et al. (2013) reported on 225 substances from the European Chemicals Agency (ECHA) database and 110 pesticide actives from Creton et al. (2010) using a 5-category GHS classification

Creton et al. 2010. Acute toxicity testing of chemicals-Opportunities to avoid redundant testing and use alternative approaches. Crit Rev Toxicol 40: 50-83
Seidle et al. 2011. Examining the regulatory value of multi-route mammalian acute systemic toxicity studies. ALTEX 28:95-102
Moore et al. 2013. Can acute dermal systemic toxicity tests be replaced with oral tests? Regul Toxicol Pharmacol 66:30-7

NICEATM Oral-Dermal LD_{50} 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

NICEATM Oral-Dermal LD_{50} Data Evaluations

- In 2013, a re-evaluation 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
  - Supplemented data set of technical pesticide active ingredients with additional compounds, current working dataset has > 250 pesticides
    - ECHA database
    - Toxic Substances Control Act (TSCA) test submissions
    - EPA Office of Pesticide Programs Reregistration Eligibility Documents (REDs)
    - Creton et al. (2010)

NICEATM Oral-Dermal LD_{50} Data Evaluations

- In 2013, a re-evaluation initiated with collaboration from EPA's Office of Pesticide Programs (cont'd)
  - Further work continues to build sufficient data set for regulatory use:
    - Adding restricted use pesticides to technical active ingredient dataset
      - A product, or its uses, classified as "Restricted Use" may only be applied by a certified pesticide applicator or under the direct supervision of a certified applicator (40CFR, Part 152.160-175)
      - http://www.epa.gov/opprd001/rup/
    - Building a dataset of acute and dermal LD_{50} data for formulations
      - Formulation LD_{50} studies used for determining PPE for pesticide handlers
      - 1000's of end use products are registered by EPA
      - Work on-going to develop strategy for compiling dataset:
        - Type of formulation: liquids, dusts, flowable concentrates, granulars, etc.
        - Timing of study

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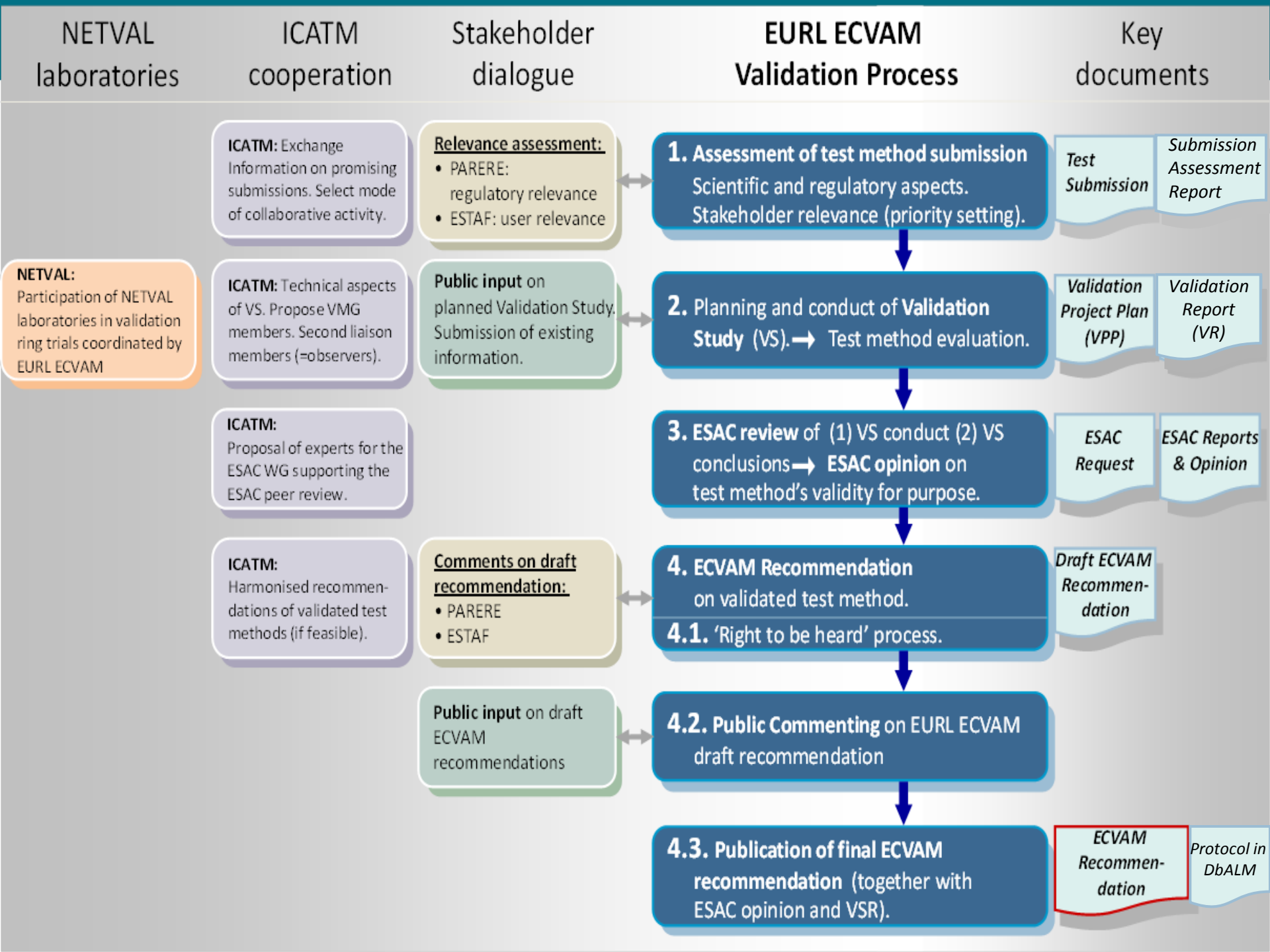
Improving Communications Role of ICCVAM

- To improve communications, ICCVAM is making plans to:
  - Improve the ICCVAM website
    - Agency-specific content on scientific efforts which are consistent with the 3Rs
    - Updated for easier navigation and to provide a venue for more transparency
  - Achieve broader engagement with the scientific community and stakeholders (e.g., the regulated community, public interest groups) though a number of different mechanisms, such as:
    - Focused workshops with well-defined objectives
    - Community of practice webinars
    - Web-based questionnaires and comment forms
    - Face-to-face forums

Improving Communications Role of ICCVAM

- Increase agency awareness of international 3R efforts
  - The US national coordinator for OECD has become an ad hoc member of ICCVAM
  - The national coordinator will provide frequent updates on topics of interest to federal agencies and will also use ICCVAM as a forum to provide feedback on those activities to OECD
  - Improved coordination with ECVAM and ICATM


NETVAL laboratories
ICATM cooperation
Stakeholder dialogue
EURL ECVAM Validation Process
Key documents
ICATM: Exchange Information on promising submissions. Select mode of collaborative activity.
Relevance assessment:
• PARERE: regulatory relevance
• ESTAF: user relevance
1. Assessment of test method submission
Scientific and regulatory aspects. Stakeholder relevance (priority setting).
Test Submission
Submission Assessment Report
NETVAL:
Participation of NETVAL laboratories in validation ring trials coordinated by EURL ECVAM
ICATM: Technical aspects of VS. Propose VMG members. Second liaison members (=observers).
Public input on planned Validation Study. Submission of existing information.
2. Planning and conduct of Validation Study (VS). → Test method evaluation.
Validation Project Plan (VPP)
Validation Report (VR)
ICATM:
Proposal of experts for the ESAC WG supporting the ESAC peer review.
3. ESAC review of (1) VS conduct (2) VS conclusions → ESAC opinion on test method's validity for purpose.
ESAC Request
ESAC Reports & Opinion
ICATM:
Harmonised recommendations of validated test methods (if feasible).
Comments on draft recommendation:
• PARERE
• ESTAF
4. ECVAM Recommendation on validated test method.
4.1. 'Right to be heard' process.
Draft ECVAM Recommendation
Public input on draft ECVAM recommendations
4.2. Public Commenting on EURL ECVAM draft recommendation
4.3. Publication of final ECVAM recommendation (together with ESAC opinion and VSR).
ECVAM Recommendation
Protocol in DbALM

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Exploring New Paradigms

- ICCVAM has recognized the need for an evolving definition / concept of “validation” that is responsive to new technologies and 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

Exploring New Paradigms

- There is significant worldwide interest in understanding how pathways become engaged in toxicity responses
- The aim is that this knowledge will lead to predictive, integrated test strategies that combine *in silico* approaches, multiple
  in vitro assays with limited, targeted testing in laboratory animals
- Various statistical approaches to assembling components of a test battery warrant consideration by ICCVAM, as well as statistical models for integrating all relevant information and assay results
- In addition, significant efforts are being put into *in silico* and *in vitro* approaches for screening and prioritization

Exploring New Paradigms

- With respect to the evolving definition / concept of "validation": ICCVAM and NICEATM have roles to play
  - These roles are being defined at this time
- ICCVAM and NICEATM is engaging the public to reconsider the concept of validation and the roles of ICCVAM and NICEATM in this new paradigm

Summary

- ICCVAM and NICEATM are making changes :
  - 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 and there is a reasonable likelihood of success with a reasonable timeframe (1 to 5 years) to implement for regulatory use
    - Maintain flexibility to reorient efforts to maximize potential progress towards use of alternative approaches
    - Long-term goal to work towards a new definition/concept of “validation” to speed up acceptance of methods and to be more responsive to on-going paradigm shifts in toxicity testing
  - Improve communications and more engagement with the scientific community, the public, and stakeholders.
  - These are initial steps and there is more work to do….

Questions for SACATM

- Please comment on the changes to the focus and priorities of ICCVAM and NICEATM as outlined in the Environmental Health Perspectives editorial 15 Years Out: Reinventing ICCVAM
- Please comment specifically on ICCVAM's strategic decisions to require a federal agency to sponsor a nomination or submission of a new method or alternative assay for ICCVAM consideration or action, and to identify priority areas for enhanced, immediate resource investment where there is an expectation of short-term success