NICEATM

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

NICEATM-ICCVAM Update

William S. Stokes, DVM, DACLAM, DACAW, BCES

RADM, U.S. Public Health Service

Executive Director, ICCVAM

Director, NICEATM

Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods

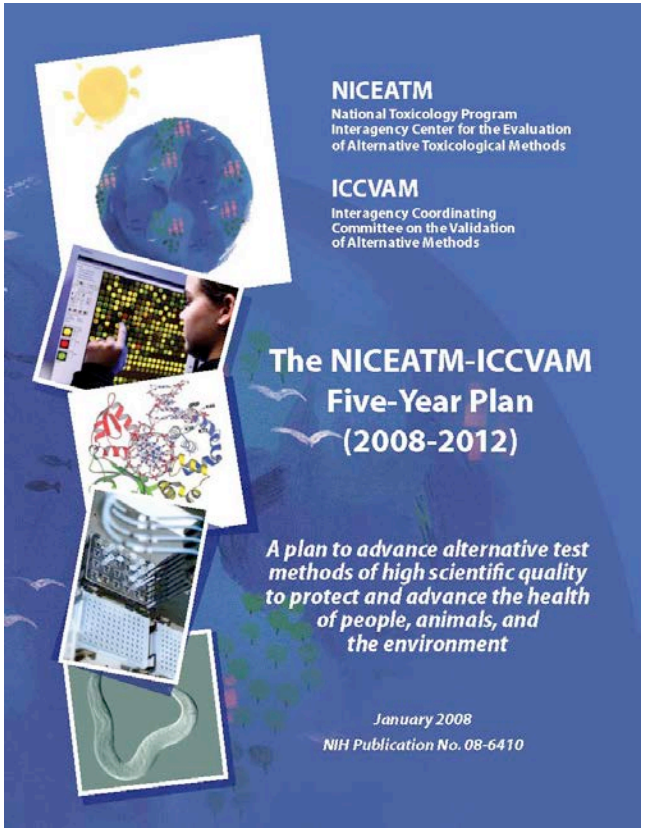
September 5, 2012

NIEHS, RTP, NC

National Toxicology Program

U.S. Department of Health and Human Services

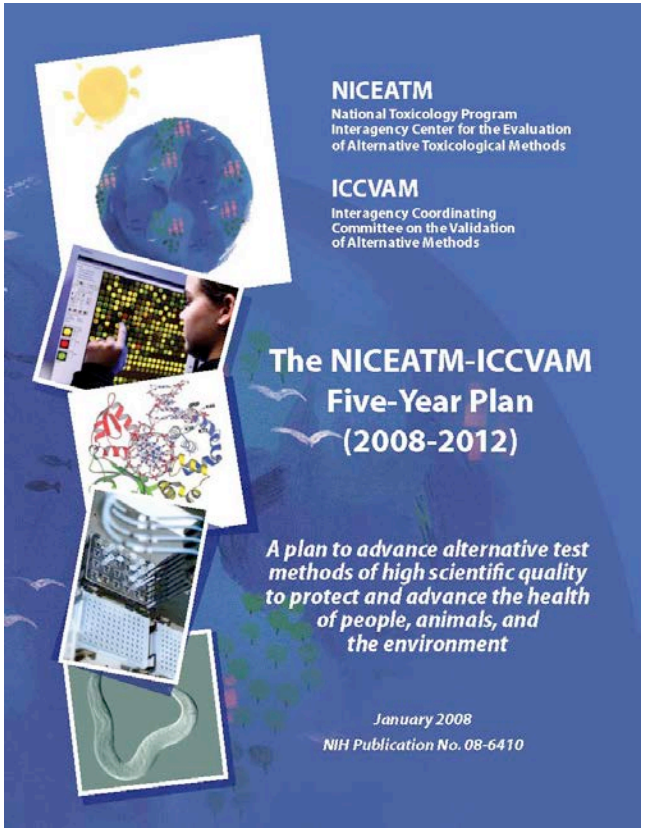
NICEATM and ICCVAM Five-Year Plan: 2008-2012



- Four strategic directions:
  - Conduct and facilitate alternative test method activities for priority test methods
  - Promote new science and technology applicable to alternative test methods
  - Foster regulatory acceptance and use of alternative test methods
  - Develop partnerships

http://iccvam.niehs.nih.gov/about/accept.htm

NICEATM and ICCVAM Five-Year Plan: 2008-2012 Priorities



- Four highest priorities:
  - Toxicity testing:
    - Accounts for 1/3 of animals used in testing
    - Highest priorities
      - Eye injuries
      - Skin injuries
      - Acute poisoning
        - Oral, dermal, inhalation
  - Vaccines and other Biologics
    - Accounts for 2/3 of animals used in testing
- Priorities based on:
  - Agency needs and priorities
  - Numbers of animals used
  - Pain and distress involved

http://iccvam.niehs.nih.gov/about/accept.htm

NICEATM and ICCVAM Progress - 1

- ICCVAM progress reported in two recent biennial reports:
  - 2008-09
  - 2010-11
- The number of adopted and available alternative test methods has tripled in the past 5 years
  - Test methods that replace, reduce, or refine animal testing
- Since 1999, 58 alternative test methods adopted:
  - 36 *in vitro* methods
  - 22 methods that use fewer animals and/or avoid or reduce pain

http://iccvam.niehs.nih.gov/

NICEATM and ICCVAM Progress - 2

- Alternative Methods for Toxicity Testing:
  - The acute “6-pack” tests are priorities:
    - Account for over 50% of animals used in toxicity testing, and account for the majority of painful procedures
    - EPA, CPSC, DOT, OSHA
  - Progress:
    - 26 alternative test methods now available
    - **Reduction:**
      - 50-60% fewer animals now required
    - **Replacement**
      - 2/6 tests can be done without animals in some cases
    - **Refinement:**
      - 3/6 tests no longer involve pain and distress, or pain is greatly reduced

http://iccvam.niehs.nih.gov/

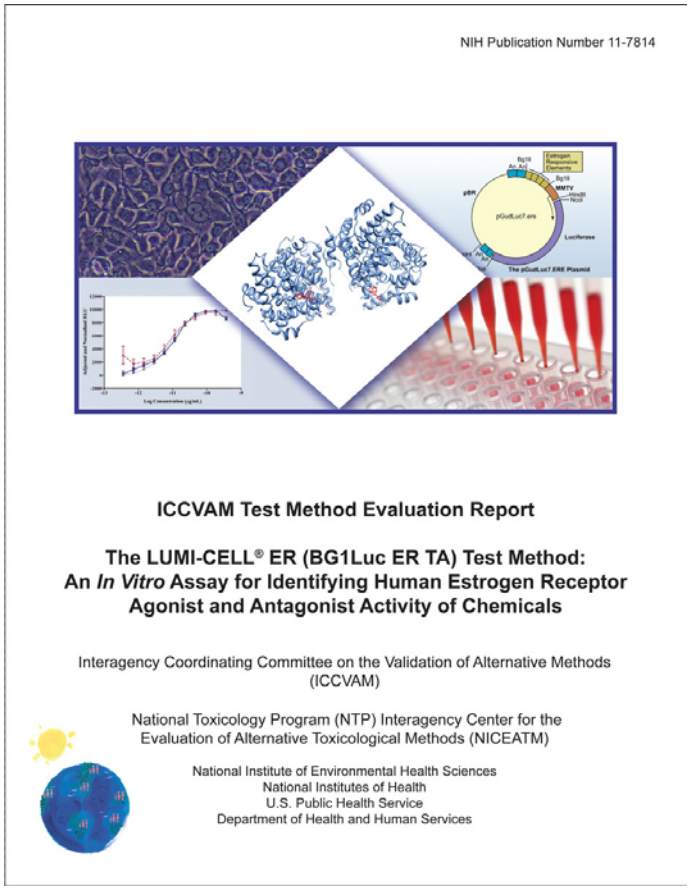
NICEATM and ICCVAM Progress - 3

- Alternative methods available for other toxicity testing areas:
  - Phototoxicity
  - Dermal absorption
  - Pyrogenicity
  - Genetic toxicity
  - Endocrine disruption

- Biologics and Vaccine Testing:
  - FDA, USDA, DHS, HHS /BARDA, DoD
  - 14 alternative test methods adopted since 1999
  - Estimated 50% of vaccines do not require animals for lot release potency testing

http://iccvam.niehs.nih.gov/

ICCVAM Test Method Evaluations: Endocrine Disruptor Chemical Screening Methods



- BG1Luc ER TA (LUMI-CELL®) stably-transfected transcriptional activation assays
  - ER agonist and antagonist protocols
  - March 2011: International Peer review
  - February 2012: Test Method Evaluation Report transmitted to Federal Agencies
  - August, 2012: Agency responses
- ICCVAM Interagency Endocrine Disruptor Working Group
  - ECVAM, JaCVAM, KoCVAM liaisons

More details in regulatory acceptance update

BG1Luc ER TA (LUMI-CELL®) Assays: Adaptation to Tox21

- 2011 - NICEATM nominated BG1 agonist and antagonist assays for testing in Tox21 High Throughput Screening (HTS)
- 2012 – Both assays adapted to the 1536 well format; data generated for the 10,000 chemical library
  - Library includes 76/78 validation study reference chemicals
- May represent a novel and efficient way to validate HTS versions of previously validated and accepted test methods

- Agenda item later today

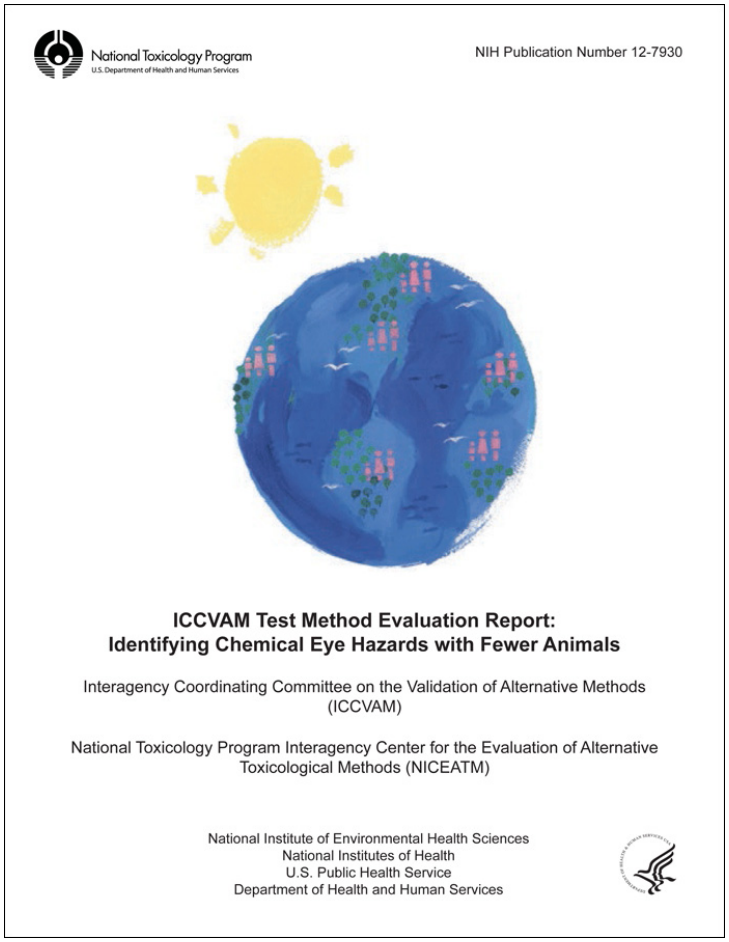
Other Endocrine Disruptor Chemical Screening Test Method Evaluations - 1

- NICEATM International Validation Study*: In Vitro* MCF-7 Cell Proliferation Assays to Detect ER Agonists and Antagonists
  - Developed by CertiChem, Inc., (NIH SBIR Grant)
  - 2011: Testing completed in U.S., Japan, Korean labs
    - Coordinated by NICEATM, participation by JaCVAM and KoCVAM sponsored labs
  - 2012: Validation study report completed
    - Under review by Study Management Team

Other Endocrine Disruptor Chemical Screening Test Method Evaluations - 2

- Validation Study: MELN ER TA Assay (ECVAM lead)
  - Agonist and antagonist assays using MELN cell line
    - Stably transfected MCF-7 human breast adenocarcinoma cell line with estrogen responsive gene coupled to luciferase reporter
    - MCF-7 cells endogenously express ER-alpha
  - NICEATM on Validation Management Group

ICCVAM Ocular Test Method Evaluation Report: Identifying Chemical Eye Hazards with Fewer Animals



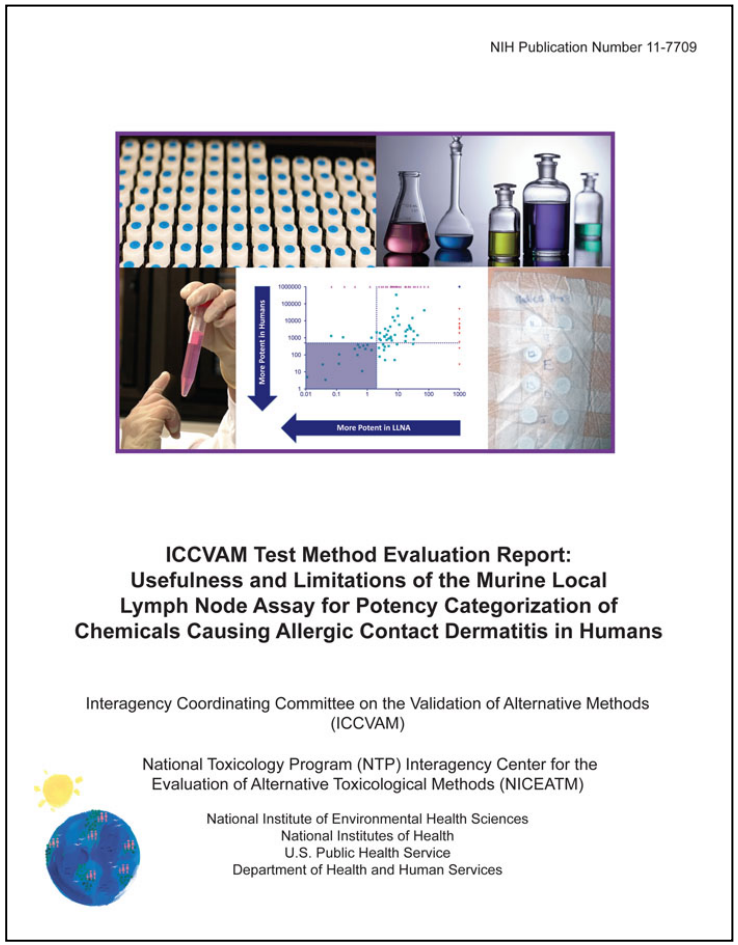
- June 2012: TMER approved by ICCVAM
- ICCVAM Recommendations:
  - Provides decision criteria for a 3-animal test that maintains ocular hazard classification equivalent to that provided by current testing procedures that use 6-18 animals
  - Reduces animal use by 50-83%
  - Harmonizes maximum number of animals used across U.S. regulatory agencies (FDA, CPSC, OSHA) and international test guidelines
- Current status: Transmittal to Federal agencies pending HHS clearance

TMER available at:
http://iccvam.niehs.nih.gov/methods/ocutox/reducenum-TMER.htm.

Current ICCVAM Ocular Toxicity Test Method Evaluations

- ICCVAM Ocular Toxicity Interagency Working Group (OTWG) coordinating evaluations
- **Short Time Exposure Test (STE),** JaCVAM validation study
  - Uses rabbit corneal epithelial cell line (SIRC cells)
  - NICEATM-ICCVAM performing additional analyses to maximize applicability in preparation for peer review
- **Isolated Rabbit Eye (IRE) Test**
  - 2005, 2009 ICCVAM Evaluations: more data needed
  - 2012: New data submitted by GSK and Harlan Labs
- **Bovine Corneal Opacity and Permeability Assay (BCOP)**
  - Updating OECD TG437 to ID some non-classified substances
- **SIRC-CVS cytotoxicity assay**: JaCVAM validation study ongoing
- July 13, 2012: FR notice requesting ocular data and nominations for peer review panel members
- 2013: Peer Review Panel meeting

ICCVAM Test Method Evaluation Report: Use of the LLNA for Potency Categorization of Skin Sensitizers

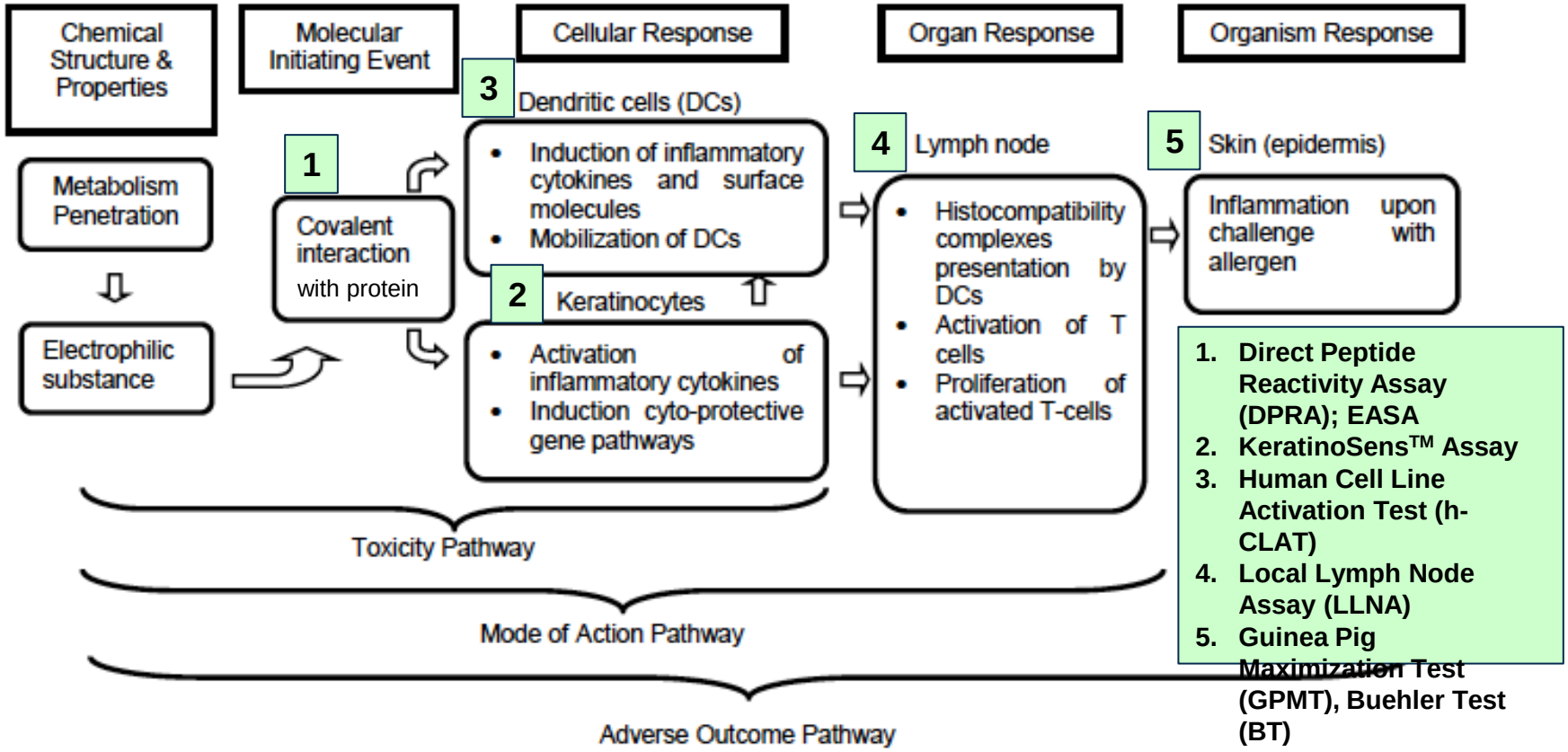


- August, 2011: Recommendations transmitted to agencies for adoption decisions
- Evaluation coordinated by ICCVAM Immunotoxicity Interagency Working Group (IWG)
- February 7, 2012: Agency responses received

More details in regulatory acceptance update

Available at:
http://iccvam.niehs.nih.gov/methods/immunotox/LLNApotency.htm

Incorporation of Adverse Outcome Pathway (AOP) Key Events in Skin Sensitization Test Methods



Adpated from: OECD. 2011. Report of the Workshop on Using Mechanistic Information in Forming Chemical Categories. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 138. ENV/JM/MONO.

NICEATM-ICCVAM: Other Allergic Contact Dermatitis Test Method Activities

- EURL-ECVAM Pre-Validation Study
  - NICEATM- ICCVAM participating on Study Management Team
  - Direct Peptide Reactivity Assay (DPRA)
    - Completed; Undergoing ESAC peer review
  - Human Cell Line Activation Test (h-CLAT)
    - Testing completion Fall 2012
  - Myeloid U937 Skin Sensitization Test (MUSST)
- JaCVAM Validation Study
  - IL-8 reporter gene assay
  - NICEATM-ICCVAM participating on Study Management Team

Developing an Integrated Testing and Decision Strategy for Skin Sensitization

- NICEATM used LLNA, DPRA, and structural reactivity (SR) (Safford et al., 2011) to evaluate 67 chemicals for skin sensitization
- Decision rules:
  - If both SR+ and DPRA+: chemicals classified as sensitizers without animal testing
    - Correctly identified 36 sensitizers, 1 false positive
  - If SR-, or SR+ and DPRA-, evaluated with the rLLNA
    - Correctly identified all remaining sensitizers and non-sensitizers
- Overall Results:
  - 99% Accuracy (66/67); 0% false negatives; 1 false positive
  - 72% reduction in animal use compared to evaluation of all chemicals in LLNA; Animal testing only required for 30/67 substances
- Next steps:
  - Evaluate expanded database
  - Evaluate ways to further reduce chemicals requiring LLNA testing

Safford, R. J., Aptula, A. O., Gilmour N. (2011). Regul. Toxicol. Pharmacol. 60(2). 218-224.

Allergic Contact Dermatitis: Test Method Nomination

- Electrophilic Allergen Screening Assay
  - Nominated by Dr. Paul Siegel, NIOSH
    - Mechanistically similar to the direct protein reactivity assay (DPRA)
    - Identifies electrophilic allergens that react with nucleophilic amino acids to form stable covalent bond
      - Considered the molecular initiating event in the Adverse Outcome Pathway leading to skin sensitization response
  - Agenda item later today

Acute Systemic Toxicity Test Method Activities - 1

NICEATM development of Up and Down Procedure (UDP) for acute dermal toxicity

- 2008-2012 Five-Year Plan project
- Oral UDP reduced animal use by 70%: Dermal UDP expected to provide similar animal reduction of 70%
- Dermal UDP Simulation studies and model development completed
- ICCVAM Acute Toxicity Interagency Working Group evaluation of UDP ongoing
- Peer review meeting: Spring 2013

Acute Systemic Toxicity Test Method Activities - 2

- Ongoing *in vitro* metabolism CYP induction validation study (EURL ECVAM lead)
  - Cryopreserved HepaRG cells
  - Cryopreserved human hepatocytes
- NICEATM and ICCVAM participating on Study Management Team

NICEATM-ICCVAM International Workshop: Vaccine Potency and Safety Testing

- Procedia in Vaccinology 5 (2011)
  - 27 manuscripts; 265 pages
- September 14-16, 2010
  - Co-organizers: ECVAM, JaCVAM, Health Canada
  - Nearly 200 scientists, 13 countries
- Human and veterinary vaccines
- Recommendations:
  - Current best practices
  - Knowledge gaps that should be addressed to advance 3Rs methods
  - Priorities for focused workshops:
    - Rabies
    - Leptospirosis
    - Pertussis vaccines
    - Diphtheria and tetanus toxoids
    - Clostridials

Vaccine Workshop report available at:
http://www.sciencedirect.com/science/article/pii/S1877282X11000245

NICEATM-ICCVAM International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing

- October 11-13, 2011
- USDA Centers for Animal Health, Ames, Iowa, USA
- Co-organized with Health Canada, JaCVAM, and ECVAM
- Reviewed state of the science for 3Rs methods for human and veterinary rabies vaccine potency testing
- Developed recommendations for current best practices and future actions to advance global replacement, reduction, and refinement methods
- August, 2012: Workshop report published in *Biologicals* 40(5): 369-381.
- Agenda item tomorrow

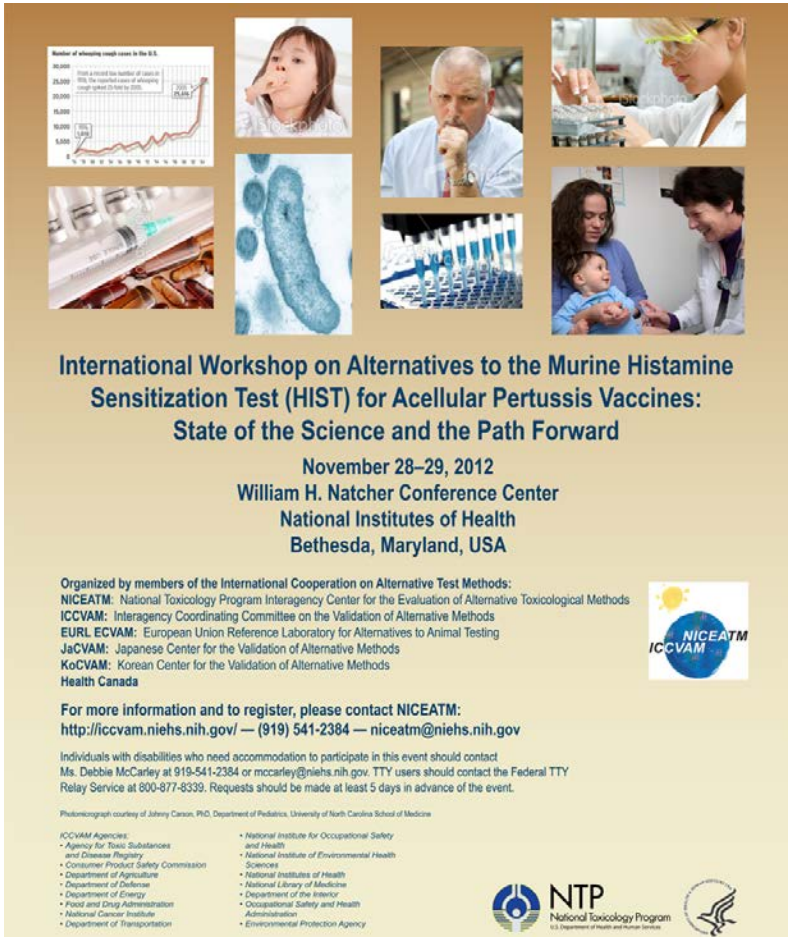
Rabies Workshop report available at:
http://www.sciencedirect.com/science/article/pii/S1045105612001066
USDA CVB Notice 12-12: http://www.aphis.usda.gov/animal_health/vet_biologics/publications/notice_12_12.pdf

NICEATM-ICCVAM Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing

- September 19-21, 2012
- USDA Centers for Animal Heath Ames, Iowa, USA
- Co-organized with ICATM partners
- Will address how to further implement replacement methods for potency testing, and how to further reduce and refine testing until complete replacement
- Workshop proceedings planned
- Agenda item tomorrow

Further information available at:
http://iccvam.niehs.nih.gov/meetings/LeptoVaccWksp-2012/LeptoVaccWksp.htm

International Workshop on Alternatives to the Murine Histamine Sensitization Test for Acellular Pertussis Vaccines



- November 28-29, 2012
- William H. Natcher Conference Center, National Institutes of Health, Bethesda, MD, USA
- Co-organized with ICATM partners
- NICEATM and ICCVAM Organizing Committee coordinating with International Pertussis Spiked Vaccine Working Group
- Will review initial data for several replacement methods; develop future validation studies needed for regulatory consideration
- Agenda item tomorrow

Additional information available at:
http://iccvam.niehs.nih.gov/meetings/HISTWksp-2012/HISTWksp.htm

2011 Pyrogen Test Method Nomination

- ICCVAM recommendations for five in vitro pyrogen tests accepted by FDA in 2009 for endotoxin detection
- Biotest AG nominated *in vitro* monocyte activation test (MAT) for detection of non-endotoxin pyrogens
- June, 2011: SACATM agreed with ICCVAM draft high priority
- August 2011: ICCVAM assigned final high priority
- Current status: Biotest (Merck KGaA) preparing comprehensive review document containing all available data
- ICCVAM Interagency Pyrogen Working Group coordination
- June, 2012: FDA Guidance for Industry: *Pyrogen and Endotoxins Testing: Questions and Answers*
  - Includes guidance on product specific validation of in vitro pyrogen tests

2011 Botulinum Neurotoxin (BoNT) Test Method Nomination - 1

- April 2011: Biosentinel nomination of three *in vitro* assays: BoTest™, BoTest™Matrix, and BoCell™
- June 2011: SACATM agreed with ICCVAM draft high priority
- August 2011: ICCVAM assigned final high priority
  - Botulism neurotoxin (BoNT) testing required by multiple Federal agencies: CDC, EPA, USDA, FDA, DoD, DHS, DoI, HHS (BARDA)
- Biosentinel continues to develop and validate their *in vitro* assays
  - Collaborations with:
    - Health Canada
    - UK Food Safety Labs
    - National Institute of Health Sciences, Division of Biomedical Food Research, Japan

Botulinum Neurotoxin (BoNT) Test Methods - 2

- ICCVAM Interagency Botulism Neurotoxin Working Group:
  - Established to focus on BoNT Test Methods; provide comments on proposed studies and communicate agency data needs to developers
  - 2013 workshop proposed in conjunction with the Interagency Botulism Research Coordinating Committee (IBRCC) Annual Meeting
    - Focus on *in vitro* methods for BoNT detection and quantification

- Related Progress:
  - Since 2006 ICCVAM Botulinum Alternatives Workshop, significant advances made in 3Rs alternatives to mouse LD_{50} assay
    - June 2011: Allergan announced FDA approval for an *in vitro* cell-based potency assay for Botox®; estimated to reduce animal use by > 95%

Outreach Activities: 8th World Congress on Alternatives and Animal Use in the Life Sciences

- August 21-25, 2011; Montreal, Canada
- Participation by NICEATM and 5 ICCVAM agencies
  - 9 Posters
  - 9 Platform presentations
  - 8 Session chairs or co-chairs
  - Satellite Meetings
    - Alternatives to the Pertussis Safety Test
    - ICATM Coordination Meeting

Presentations available at: http://iccvam.niehs.nih.gov/meetings/8WC/8WCablst.htm

Outreach Activities:
2012 Society of Toxicology Annual Meeting

- March 11-15, 2012
- San Francisco, CA
- 7 Posters Presented
- Satellite Meeting
  - ICATM Coordination Meeting

SOT posters available at: http://iccvam.niehs.nih.gov/meetings/SOT12/sotablst.htm

Outreach Activities: Selected Additional NICEATM-ICCVAM Presentations

- NY Academy of Sciences Workshop: Animal Models and Their Value in Predicting Drug Efficacy and Toxicity
- World Congress on *In Vitro* Biology
- FDA Office of the Commissioner Pre-Clinical Review Lecture Series
- JaCVAM Scientific Advisory Committee Meeting
- ECVAM Scientific Advisory Committee Meetings
- North Carolina Workshop on Laboratory Animal Medicine
- 24th Annual Meeting of Japanese Society for Alternatives to Animal Experiments
- JSAAE Workshop on Adverse Outcome Pathways (Sept 13, 2012)
- AIMBE/NIBIB Workshop on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process (September 17-18, 2012)
- ILSI-HESI Workshop on Using Stem Cells for Cardiotoxicity Models (November, 2012)

Other NICEATM-ICCVAM Communications: 2011-2012

- 20 “ICCVAM-all” listserv e-mail announcements
  - 900+ member list of ICCVAM stakeholders
  - Announcements of events, publications, funding opportunities, etc.
- 12 NIEHS *Environmental Factor* newsletter articles
- Quarterly NTP Update and ALTEX news articles
- 17 *Federal Register* notices

Time period covered: June 17, 2011-August 29, 2012

Draft 2013-2017 NICEATM-ICCVAM Five-Year Plan


The NICEATM-ICCVAM Five-Year Plan
(2013-2017)

A plan to advance innovative test methods of high scientific quality to protect and improve the health of people, animals, and the environment

DRAFT: May 14, 2012

Prepared by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

A plan to advance innovative test methods of high scientific quality to protect and improve the health of people, animals, and the environment

- Developed by NICEATM and the 15 ICCVAM Federal agencies
- Provides strategic direction for NICEATM and ICCVAM to accomplish their purposes, duties, and mission during 2013-2017
- Implementation plan in development
- June 13, 2012: Draft plan available for public review and stakeholder comment
- January 2013: Symposium - Transforming 21st Century Safety Testing: Advancing Science, Public Health, and Animal Welfare
- Agenda item today

Available at:
http://iccvam.niehs.nih.gov/docs/5yearplan.htm

NICEATM

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

Regulatory Acceptance and Availability of ICCVAM-Recommended Alternative Test Methods

William S. Stokes, DVM, DACLAM, DACAW, BCES

RADM, U.S. Public Health Service

Executive Director, ICCVAM

Director, NICEATM

Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods

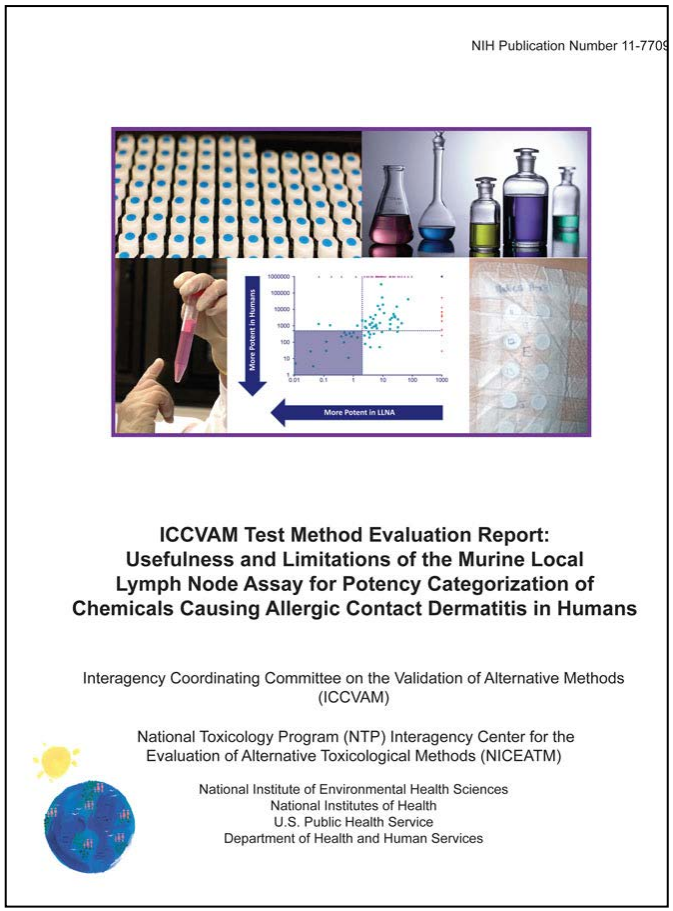
September 5, 2012

NIEHS, RTP, NC

National Toxicology Program

U.S. Department of Health and Human Services

Regulatory Acceptance:
Use of the LLNA for Potency Determination



February, 2012: Federal Agencies accepted ICCVAM recommendations:

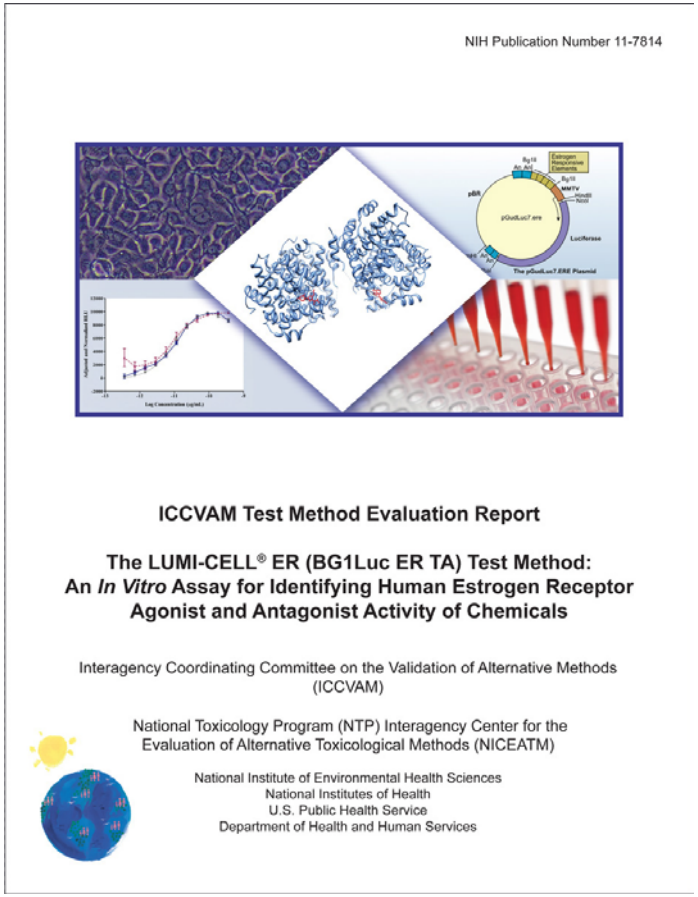
- LLNA can be used to categorize strong sensitizers using EC3 < 2
- Substances that do not meet the criterion (EC3>2) require additional testing or information to determine they are not strong skin sensitizers
- Strong sensitizers = substances with significant potential for causing allergic contact dermatitis (CPSC)
- ICCVAM evaluation based on comparing LLNA results to human clinical studies

Available at:
http://iccvam.niehs.nih.gov/methods/immunotox/LLNApotency.htm

LLNA for Potency Determination: Impact on 3Rs

- Can now be used instead of GPMT to assess potency of sensitizing chemicals
- Impact on 3Rs:
- Reduction:
  - 33% fewer animals (20 vs. 30 or more), using the 3-dose LLNA
- Refinement:
  - Completely avoids pain and distress:
    - Avoids pain and distress associated with a positive reaction in guinea pigs
    - Avoids irritating adjuvants used in GPMT

Regulatory Acceptance: BG1Luc ER TA (LUMI-CELL®) to Identify Human ER Agonist/Antagonist Activity of Chemicals



ICCVAM final recommendations:

- *"The BG1Luc ER TA test method can be used as a screening test to identify substances with in vitro estrogen receptor agonist activity"*
- *"The BG1Luc ER TA test method can be used as a screening test to identify substances with ER antagonist activity"*
- *"The accuracy of this assay is at least equivalent to that of EPA OPPTS Test Guideline 890.1300, part of the EDSP Tier 1 screening battery"*

BG1 TMER:
http://iccvam.niehs.nih.gov/methods/endocrine/ERTA-TMER.htm

US Federal Agency Responses to ICCVAM (Selected): Recommendations on BG1Luc ER TA

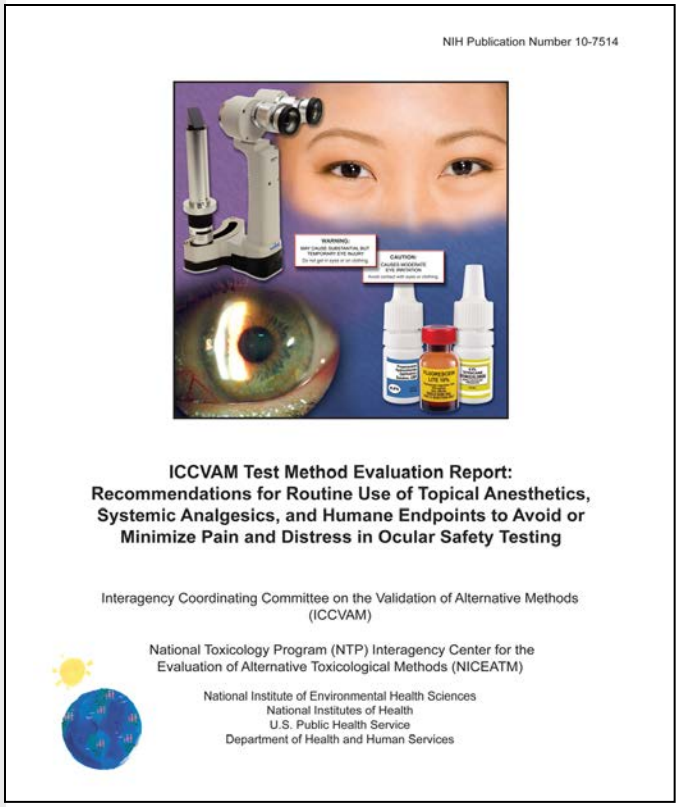
- EPA: "*The EPA regards the BG1Luc assay as an alternative to the OCSPP 890.1300 test guideline for transcriptional activation currently used in the EPA's Endocrine Disruptor Screening Program*."
- CPSC: "*Information from the LUMI-CELL® assay may be invaluable when determining whether a compound is a chronic hazard in a Weight-of-evidence approach. The assay may also provide supporting information that reduces the need to use a full complement of test animals to determine whether a chemical or substance is a chronic hazard*."
- BG1Luc ER TA Impact on 3Rs:
  - Reduction: A negative result in the Tier I test battery is sufficient to classify a chemical as having low or no potential to cause endocrine disruption, thus avoiding Tier II animal tests

Transmittal of BG1 to Federal agencies and their responses
http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm#agencyresponses

BG1Luc ER TA (LUMI-CELL®): OECD Test Guidelines

- New Test Guideline - TG 457: "BG1Luc Estrogen Receptor Transactivation Test Method for Identifying Estrogen Receptor Agonists and Antagonists"
  - Accompanying Performance Standards
- Updated TG 455: "Stably Transfected Human Estrogen Receptor-α Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals"
  - Based on the CERI-STTA and BG1Luc ER TA methods
  - First OECD Performance-Based Test Guideline
  - Accompanying Performance Standards
- Status:
  - April 2012: Approved at WNT Meeting
  - July 2012: Endorsed by Joint Meeting and Environmental Policy Committee
  - September 2012 (expected): Formal OECD adoption

ICCVAM Recommendations to Refine Ocular Safety Testing: International Acceptance



- Routine use of analgesics, topical anesthetics, and humane endpoints for required *in vivo* ocular safety testing
- Eliminates most if not all pain and distress for eye safety testing while and where in vivo testing is still required
- Adopted by US agencies in 2011
- Included in updated OECD Test Guideline 405: Acute Eye Irritation/Corrosion
  - April 2012: Updated TG Approved at WNT Meeting
  - September 2012 (expected): Formal OECD adoption

Available at:
http://iccvam.niehs.nih.gov/methods/ocutox/OcuAnest-TMER.htm

Ocular Safety Testing: International Acceptance

- Guidance Document 160:
  - *The Bovine Corneal Opacity And Permeability (BCOP) and Isolated Chicken Eye (ICE) Test Methods: Collection of Tissues for Histological Evaluation and Collection of Data on Non-severe Irritants*
  - Submitted by NICEATM-ICCVAM to encourage use of histopathology as additional endpoint for *in vitro* ocular safety methods and expand data available for future evaluation of value in increasing accuracy of ICE and BCOP
  - Supplement to TG 437 (BCOP) and TG 438 (ICE)
  - OECD adoption: October 25, 2011

Available at:
http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=ENV/JM/MONO(2011)45&doclanguage=en

Acknowledgements: Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Agency for Toxic Substances and Disease Registry

* Moiz Mumtaz, PhD
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Eric J. Sampson, PhD

Consumer Product Safety Commission

* Joanna Matheson, PhD, **Vice-Chair**
\+ Kristina Hatlelid, PhD

Department of Agriculture

* Jodie Kulpa-Eddy, DVM, **Chair**
\+ Carol Clarke, DVM, DACLAM

Department of Defense

* Patrick Mason, PhD (DRE)
\+ Terry Besch, DVM, DACLAM, DACVPM, (USAMRIID)
\+ Patty Decot (DRE)

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Department of the Interior

* Barnett A. Rattner, PhD

Department of Transportation

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\+ Alternate Principal Agency Representative

Environmental Protection Agency

Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention

* Anna Lowit, PhD

NHERRL, *Office of Research and Development*

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National Institute for Occupational Safety and Health

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Vasant Malshet, PhD, DABT
Center for Food Safety and Nutrition
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