

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

*Interagency Coordinating Committee on
the Validation of Alternative Methods*



NICEATM and ICCVAM Update

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Director, NICEATM
Executive Director, ICCVAM**

**5th Meeting of the Scientific Advisory Committee
on Alternative Toxicological Methods**

December 12, 2005

Alexandria, VA

Outline

- **NICEATM and ICCVAM Test Method Evaluation Activities**
 - Ocular Toxicity
 - Acute Systemic Toxicity
 - Endocrine Disruptor Test Methods
 - Ocular and Dermal Test Methods for Anti-Microbial Disinfectant Products

- **Other Activities and Collaborations**
 - 5th World Congress on Alternatives and Animal Use in the Life Sciences
 - ECVAM
 - OECD
 - JaCVAM



Additional NICEATM and ICCVAM Updates

- **ICCVAM Nominations and Submissions, Dr. Tice**
 - *In Vitro* Pyrogenicity tests (5)
 - Botulinum toxin potency testing

- **Performance Characteristics of the *In Vivo* Ocular Irritancy Test, Dr. Haseman**

- **Independent Evaluation of Four *In Vitro* Test Methods to Identify Ocular Corrosives and Severe Irritants: Report from the Expert Panel, Dr. Freeman**

- **ICCVAM/NICEATM/ECVAM Workshop on Validation Principles and Approaches for Toxicogenomic-Based Methods, Dr. Schechtman**

- **ICCVAM-NICEATM-ECVAM Ocular Toxicity Scientific Symposia, Dr. Stokes**
 - Mechanisms of Chemically Induced Ocular Injury and Recovery
 - Minimizing Pain and Distress in Ocular Safety Testing



Ocular Toxicity Test Methods

- **ICCVAM Evaluation of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants**
 - Bovine Corneal Opacity and Permeability (BCOP) Test
 - Hen's Egg Test - Chorion Allantoic Membrane (HET-CAM)
 - Isolated Rabbit Eye (IRE) Test
 - Isolated Chicken Eye (ICE) Test

- **Evaluation Process**
 - Coordinated by ICCVAM Ocular Toxicity Working Group
 - Support from NICEATM
 - Liaison members from ECVAM
 - Comprehensive Background Review Documents prepared for each method
 - Based on published literature and data submitted in response to 2 public calls for data and information
 - Released to public, November 2004



Organizations Contributing *In Vivo/In Vitro* Eye Irritancy Data

- Cosmetics, Toiletries, and Fragrances Association (CTFA)
- European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)
- European Centre for the Validation of Alternative Methods (ECVAM)
- ExxonMobil
- GlaxoSmithKline
- Institute for In Vitro Sciences
- Japanese National Institute of Health Sciences
- Procter & Gamble
- S.C. Johnson
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- ZEBET



Ocular Toxicity Test Methods



ICCVAM The Interagency Coordinating Committee on the Validation of Alternative Methods

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

Expert Panel Meeting to Assess the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants:

Bovine Corneal Opacity and Permeability (BCOP)
Hen's Egg Test - Chorioallantoic Membrane (HET-CAM)
Isolated Chicken Eye (ICE)
Isolated Rabbit Eye (IRE)

January 11-12, 2005
National Institutes of Health
Natcher Conference Center, Bethesda, Maryland

 **ICCVAM NICEATM**
Protecting and advancing the health of people, animals, and our environment.

ICCVAM Agencies:
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 Cancer Institute
National Institute of Environmental Health Sciences • National Institutes of Health, Office of the Director • National Institute for Occupational Safety and Health
National Library of Medicine • Occupational Safety and Health Administration



■ Expert Panel Meeting: January 11-12, 2005, Bethesda, MD

- Panel Report
 - Public availability and comments requested
 - *FR*, 70(53):13513-4, 03/21/05
- Second request for data
 - Based on comments that additional data were available
 - (*FR*, 70(38): 9661, 02/28/05)

All Ocular BRDs and Panel Reports available at:

<http://iccvam.niehs.nih.gov/methods/eyeirrit.htm>



Ocular Toxicity Test Methods

2005: Post-meeting addendum to BRDs

- | | |
|--------------|---|
| March 30 | Additional ocular data due to NICEATM in response to February 28, 2005 FR notice |
| April - June | NICEATM staff revised accuracy and reliability analyses for all four test methods |
| July 26 | Availability of Draft Addendum to the Test Method BRDs and request for public comments (<i>FR</i> , Vol. 70, No. 142, pg. 43149, 07/26/05) |
| September 19 | Second Expert Panel Meeting <ul style="list-style-type: none">• Held via Public Teleconference |
| November 2 | Availability of Second Expert Panel Report and request for public comments (<i>FR</i> , Vol. 70, No. 211, pg. 66451, 11/02/05) |

2006

- | | |
|----------------|---|
| February-March | ICCVAM Test Method Evaluation Report and Final BRDs |
|----------------|---|



In Vitro Acute Systemic Toxicity Test Methods

- **NICEATM-ECVAM Joint Independent Validation Study**
 - Initiated in response to recommendations from the October 2000 ICCVAM *International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity*
 - 2 cytotoxicity test methods
 - NHK NRU
 - 3T3 NRU
 - 3 labs
 - US Army, Edgewood Laboratory
 - Bioreliance/ Institute for In Vitro Sciences
 - University of Nottingham
 - 72 chemicals
 - Lab studies completed January 2005
 - BRD in final stages of preparation



In Vitro Acute Systemic Toxicity Test Methods

■ Study Objectives

- 1) Standardize two *in vitro* basal cytotoxicity test method protocols
- 2) Evaluate intra- and inter-laboratory reproducibility
- 3) Assess the accuracy of the *in vitro* cytotoxicity assays for:
 - Estimating rodent oral LD50 values
 - Identifying rodent acute oral toxicity GHS hazard categories
 - Estimating human lethal blood IC50s
- 4) Provide a high quality basal cytotoxicity database that can be used to determine what additional *in vitro* test methods will be necessary to accurately estimate rodent acute oral toxicity hazard categories
- 5) Determine the usefulness and limitations of using cytotoxicity IC50 data as the basis for starting doses for *in vivo* acute toxicity studies, and the extent that this will reduce and refine animal use.



In Vitro Acute Systemic Toxicity Test Methods

■ Timeline for Evaluation

- February 2006 - FR notice announcing Peer Panel meeting; availability of draft BRD for review and comment
- May 23, 2006 - Independent Peer Review Panel meeting, Bethesda, MD
- Summer 2006 -
 - Panel Report published; public comments requested
- Fall 2006 -
 - Final ICCVAM Test Method Evaluation Report



Acute Systemic Toxicity Test Methods (3)

ICCVAM Acute Toxicity Working Group

CPSC

Patricia Brundage
Kailash Gupta
Marilyn Wind

DOE

Po-Yung Lu

EPA

Karen Hamernik, OSCP
Masih Hashim, OPP
Marianne Lewis, OPPTS
Elizabeth Margosches, OPPT
Debbie McCall, OPP
John Redden, OPPTS
Amy Rispin, OPP

FDA

Leonard Schechtman, NCTR
Kenneth Hastings, CDER
Abigail Jacobs, CDER
Suzanne Morris, NCTR
David Morse, CDER
Thomas Umbreit, CDRH

NIEHS

Rajendra Chhabra
William Stokes
Raymond Tice

NIOSH

Steven Reynolds



Endocrine Disruptor Test Methods

■ LUMI-CELL™ ER Screening Assay

- Stably-transfected transcriptional activation assay
- Detects agonist and antagonist activity
- Nominated for validation studies
- NICEATM modified support contract to fund standardization studies for this assay
 - **Standardization Study Initiated September, 2005**
 - **Completion expected: June 2006**

■ International Independent Validation Study

- 3 laboratories: US, Japan, Europe
- Study Management Team to include ECVAM and JaCVAM



Endocrine Disruptor Test Methods

- **Reference Substances Recommended for *In Vitro* ED Validation Activities**
 - Originally proposed in ICCVAM Test Method Evaluation Report (NIH Pub. 03-4503)
 - Based on 2002 Expert Panel Meeting
 - Common list of 78 substances for both ER and AR methods
 - **ER methods: 53 minimum substances**
 - **AR methods: 44 minimum substances**
 - NICEATM and ICCVAM Endocrine Disruptor Working Group currently revising list
 - Revised list will address availability and cost issues



Ocular and Dermal Test Methods for Antimicrobial Disinfectant Products

2004

- June 21** NICEATM received letter from EPA Director of Office of Pesticide Programs (OPP)
- EPA's Pesticide Program Dialogue Committee (PPDC) developing non-animal approaches for assessing skin and eye irritation potential for anti-microbial disinfectant products
 - Requested ICCVAM technical review of the approach
- August** ICCVAM recommendations:
- Development of these methods is important and should proceed with high priority
 - Most efficient approach is to coordinate independent expert panel review of a Background Review Document (BRD) of all available data documenting accuracy and reliability of these methods for their intended purpose
 - Industry should coordinate development of BRD with NICEATM and ICCVAM Ocular/Dermal Working Groups



Ocular and Dermal Test Methods for Antimicrobial Disinfectant Products (2)

2004

- October **Presented ICCVAM recommendations to SACATM**
- SACATM endorsed

2005

- March 21 **FR notice published**
- Requested data on non-animal methods and nominations for an independent expert panel

Spring-Fall

Testing and BRD Development by Industry and IIVS

- *Additional testing conducted*
- *First round data analysis*
- *Planned testing completed*
- *Second round data analysis*

- Nov 14 **PPDC representatives presented project update to ICCVAM**



Ocular and Dermal Test Methods for Antimicrobial Disinfectant Products (3)

2006--tentative schedule

January **Scheduled submission of the BRD to ICCVAM**

Spring NICEATM/ICCVAM WGs work with PPDC representatives to review submission documents for completeness.

FR notice

- Announcing availability of completed BRD and the upcoming independent expert panel meeting

Fall **ICCVAM Independent Expert Panel meeting**

Expert panel report released for public comment

Expert panel report, public comments, and proposed ICCVAM recommendations presented to the EPA Science Advisory Panel (SAP) for comment

2007

Spring ICCVAM final recommendations and Evaluation Report forwarded to Federal Agencies (per P.L. 106-545)

EPA consideration and implementation of ICCVAM and SAP recommendations



5th World Congress on Alternatives and Animal Use in the Life Sciences (1)

- **Berlin, Germany - August 21-25, 2005**
 - 600+ participants
- **7 ICCVAM Agencies Represented (NIH, NIEHS, FDA, EPA, CPSC, USDA, NLM)**
- **21 ICCVAM Agency and NICEATM Staff Attended**
 - 18 Presentations
 - 13 Posters
 - 9 Sessions Co-chaired
- **Plenary Address: Dr. Norka Ruiz Bravo, NIH Deputy Director for Extramural Research**



5th World Congress on Alternatives and Animal Use in the Life Sciences (2)

- **Satellite Meeting participation by ICCVAM/ECVAM:**
 - **2nd International Conference on Humane Endpoints in Animal Experiments for Biomedical Research**
August 20–21, 2005
 - **Practical Training on *In Vitro* Eye Irritation Methods, ZEBET**
August 26, 2005



NICEATM and ICCVAM

Collaborations with ECVAM

- **ICCVAM-NICEATM-ECVAM Workshop: *Validation Principles and Approaches for Toxicogenomic-based Methods***
 - December 2003, Ispra, Italy
 - Co-chaired by Len Schechtman(FDA, ICCVAM) and Raffaella Corvi (ECVAM)
 - Details will be presented in an upcoming agenda session
- **ECVAM Eye Irritation Expert Meeting**
 - February 8-11, 2005, Ispra, Italy
 - Participation by ICCVAM and NICEATM representatives



NICEATM and ICCVAM

Collaborations with ECVAM (2)

- **Evaluation of Ocular Toxicity Assays**
 - ICCVAM and ECVAM Sharing Data
 - Coordinated Expert Panel Reviews
 - Liaisons:
 - ICCVAM Ocular Toxicity Working Group
 - ECVAM Ocular Irritation Task Force
- **Joint NICEATM-ECVAM *In Vitro* Cytotoxicity Independent Validation Study**
- **ECVAM Acute-Tox Project**
 - NICEATM liaison



OECD Activities

■ OECD Test Guideline 435: *In Vitro* Membrane Barrier Test Method for Skin Corrosion

- Based on validated and accepted Corrositex® Test Method
- Draft TG submitted by ICCVAM to OECD in 2003
- Incorporates ICCVAM Performance Standards
- Adopted by OECD in 2005
- Available (for a fee) at: <http://www.oecd.org>



OECD Activities (2)

■ Guidance Document No. 34:

The Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment

- ICCVAM, NICEATM, ECVAM, SACATM, and ESAC representatives played key roles in the development of this document
- Culmination of 9 years effort following the 1996 OECD Solna Workshop on Validation and Regulatory Acceptance
- US hosted expert consultation meeting, October 2004
- OECD adopted, August 2005
- Provides internationally harmonized principles and processes for the validation and acceptance of animal and non-animal test methods for regulatory hazard assessment



OECD Activities (3)

■ OECD Non-Animal Testing Validation Management Group, Task Force on Endocrine Disruptors Testing and Assessment

- Functions to provide advice and coordination for related international validation studies

NICEATM/ICCVAM representative

- Communication of ICCVAM recommendations/activities:
 - Reference chemicals for validation of in vitro ED methods
 - Essential Test Method Components for in vitro ED test method protocols
 - Joint Validation study with ECVAM and JaCVAM
- 2nd meeting: Paris, November 4-5, 2004
- 3rd meeting: Paris, December 14-15, 2005



OECD Activities (4)

- Advisory Document of the Working Group on GLP: Application of GLP to In Vitro Studies
 - Adopted and Published November, 2004
 - Available as No. 14 in the Series on Principles of Good Laboratory Practice and Compliance Monitoring
 - ICCVAM-NICEATM-ECVAM contributors



Collaborations with JaCVAM

- **Japanese Center for the Validation of Alternative Methods (JaCVAM)**
 - Established at the Japanese National Institute of Health Sciences
 - Dedication Ceremony December 1, 2005
 - 19th meeting of the Japanese Society for Alternatives to Animal Experimentation
 - Drs. Stokes, Schechtman and Hartung participated
 - Initial collaboration will be a joint validation study
 - *In vitro* endocrine disruptor methods



JaCVAM Establishment, 2005



ICCVAM Agency Representatives*

ATSDR	Moiz Mumtaz	FDA	Leonard Schechtman, NCTR (Chair) Suzanne Fitzpatrick, ORA Abigail Jacobs, CDER Raju Kammula, CDRH Melvin Stratmeyer, CDRH Richard McFarland, CBER Ying Huang, CBER David Hattan, CFSAN Robert Bronaugh, CFSAN Devaraya Jagannath, CVM M. Cecilia Auguila, CVM William Allaben, NCTR Lawrence D'Hoostelaere, ORA
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DOD	Robert E. Foster Patty Decot Harry Salem John Frazier		
		NCI	Alan Poland
DOE	Marvin Stodolsky	NIEHS	William Stokes John Bucher Rajendra Chhabra Jerrold Heindel
DOI	Barnett Rattner Sarah Gerould		
DOT	George Cushmac Steve Hwang	NIOSH	Paul Nicolaysen Murali Rao
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Thank you for your attention!

