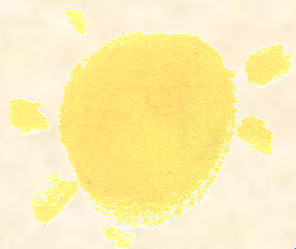


# NICEATM

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

# ICCVAM

Interagency Coordinating Committee  
on the Validation of Alternative  
Methods



## Update on NICEATM and ICCVAM Activities

William S. Stokes, D.V.M., D.A.C.L.A.M.  
Director, NICEATM

4th Meeting of the Scientific Advisory  
Committee on Alternative Toxicological  
Methods

October 20, 2004  
Research Triangle Park, NC



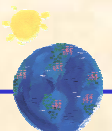
ICCVAM  
NICEATM



# Outline

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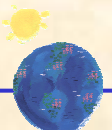
- **Test Method Evaluation Activities**
  - Ocular Toxicity
  - Endocrine Disruptors
  - Biomarkers
  - Acute systemic toxicity
  - Dermal toxicity
- **OECD Activities**
- **ECVAM Collaborations**
- **Other**



# Additional ICCVAM and NICEATM Updates

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- **Evaluation of the Under-Prediction Rate for the Rabbit Dermal Irritation Test -- *W. Stokes and J. Haseman***
- **Preliminary Evaluation of the Under-Prediction Rate for the Rabbit Ocular Irritation Test -- *W. Stokes and J. Haseman***
- **ICCVAM Nominations -- *W. Stokes***
- **ICCVAM Perspectives on Proposed OECD Draft Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (Guidance Document No. 34) -- *L. Schechtman***



# Ocular Toxicity Test Methods

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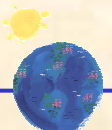
- **Background Review Documents in preparation by NICEATM and ICCVAM Ocular Toxicity Working Group (OTWG)**
  1. **Bovine Corneal Opacity and Permeability (BCOP) Test**
  2. **Hen's Egg Test - Chorio- Allantoic Membrane (HET-CAM)**
  3. **Isolated Rabbit Eye (IRE) Test**
  4. **Isolated Chicken Eye (ICE) Test**
- **Expert Panel Meeting: January 11-12, 2005**
  - **NIH Natcher Conference Center, Bethesda, MD**
- **Symposium on Mechanisms of Chemically-induced Ocular Injury and Recovery, May 10-11, 2005**
- **Symposium on Humane Approaches to Ocular Irritancy Testing, May 12, 2005**



# Ocular Toxicity Test Methods

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- **Timeline for review of in vitro methods for identifying severe and irreversible ocular irritants and corrosives:**
- **April - October 2004:**
  - Evaluate data/information received in response to *FR* notices
  - Incorporate data/information from contacted experts
  - Complete the 4 draft BRDs, including review/approval by OTWG and ICCVAM
  - Organize Expert Panel Meeting
- **November 1, 2004:**
  - *FR* notice announcing the expert meeting and the availability of the draft BRDs for review and comment
- **January 11-12, 2005:**
  - Ocular Toxicity Expert Panel Meeting, NIH Campus, Natcher Conference Center, Bethesda, MD
- **April 2005:**
  - Expert Panel Meeting report published; *FR* notice announcing report availability and requesting public comment



# Ocular Toxicity Test Methods

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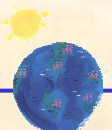
- **Federal Register notice (69(57):13859-61; 03/24/04)**
  - Comments requested on nomination of *in vitro* ocular toxicity methods and related activities
  - Data requested for chemicals evaluated by *in vitro* or *in vivo* ocular irritancy test methods
  - Comments/data due May 24, 2004
- **FR notice responses**
  - CTFA - *in vivo* data, 43 formulations
  - NIHS, Japan (Dr. Ohno) - *in vivo* data, 17 substances
  - P&G - summary info and comments
  - U. Barcelona (Dr. Vinardell) - summary info, comments, and reprints
  - Vincience - reprints



# Ocular Toxicity Test Methods

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- Requested nomination of experts for the evaluation of *In vitro* test methods for identifying potential ocular irritants
  - *Federal Register*, Vol. 69, No. 77, pp. 21565, 04/21/04
  - Nomination deadline June 7, 2004
  - 67 nominations received
  - Anticipate 24 panel members

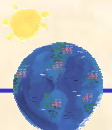


# ***In Vitro* Endocrine Disruptor Test Methods**

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- ***Federal Register Notice***

**Requested Comments and Nominations on *In Vitro* Endocrine Disruptor Screening Assays (Vol. 69, No. 77, pp. 21564, 04/21/04)**



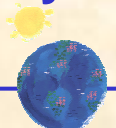


# ***In Vitro* Endocrine Disruptor Test Methods**

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## ***NICEATM Pre-screen Evaluations***

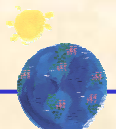
- **XDS, Inc. LUMI-CELL™ ER Screening Assay**
  - NICEATM evaluated submission for validation studies
  - EDWG evaluated and developed recommendations
  - ICCVAM recommendations will be presented later in the meeting
- **Otsuka Pharmaceutical Company, Ltd.**
  - Submitted pre-validation data from their AR TA assay to NICEATM
  - NICEATM currently reviewing for possible validation study nomination



# Biomarkers

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- **ILSI HESI Biomarkers Committee**
  - 3 HESI Working Groups developing validation study plans for:
    1. Inhibin B as a biomarker of testicular toxicity
    2. Serum Cardiac Troponins
    3. Nephrotoxicity biomarkers
  - Requested ICCVAM input on validation study plans
- **ICCVAM Created Biomarkers Working Group**
  - HESI submitted Inhibin B study plan to ICCVAM BWG
    - comments and submitted to HESI
  - Serum Cardiac Troponins and Nephrotoxicity Biomarkers study plans will be submitted to ICCVAM in the near future



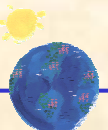
# **Acute Systemic Toxicity**

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## **NICEATM/ECVAM *In Vitro* Cytotoxicity Validation Study**

### **Timeline**

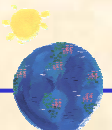
<b>Milestones</b>	<b>Expected Date</b>
<b>Lab Testing Complete</b>	<b>December 2004</b>
<b>Final Lab Reports</b>	<b>February 2005</b>
<b>Background Review Document</b>	<b>August 2005</b>
<b>Peer Review</b>	<b>October 2005</b>



# Dermal Irritation (1)

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- **ECVAM Dermal Irritation Validation Study: candidate chemicals for phase II**
  - **638 TSCATS reports and 45 Cosmetic Ingredient Review reports evaluated by NICEATM to date**
  - **42 commercially available chemicals with individual animal dermal irritation data identified**
    - **Considered potentially useful for Phase II of the ECVAM validation study**
    - **Only 12 of the 42 candidate chemicals have purity information (10 non-irritants + 2 mild irritants),**
    - **Purity information requested from EPA and/or the study sponsor for 30 candidate chemicals but appears unavailable**

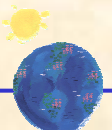


# Dermal Irritation (2)

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## ECVAM Dermal Irritation Validation Study: False Negative Corrosive Chemical Considerations

- In the ECVAM *in vitro* dermal corrosivity test method validation studies, several corrosive chemicals tested as false negatives in:
  - Corrositex™
  - The Rat Skin TER Assay
  - EPISKIN™/EpiDerm™
- No corrosives included in dermal irritation study
- Regulatory authorities will likely expect false negatives to be accurately identified by *in vitro* assays proposed as full or partial replacements for the animal test
- ECVAM Management Team
  - Issue considered important
  - These chemicals will be evaluated in a post-validation study

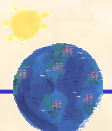


# Dermal Irritation (3)

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## ECVAM Dermal Irritation Validation Study: ICCVAM Recommendations

- Corrosive chemicals that are false negatives in *in vitro* corrosivity tests need to be evaluated in *in vitro* dermal irritation test methods during validation studies
- DCIWG currently developing a study design for testing the false negative corrosive chemicals and creating a list of chemicals to be tested





## Recommended Performance Standards for *In Vitro* Test Methods for Skin Corrosion

Prepared by the  
Interagency Coordinating Committee on the  
Validation of Alternative Methods (ICCVAM)  
and the

National Toxicology Program (NTP) 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

# Recommended Performance Standards for *In Vitro* Test Methods for Skin Corrosion

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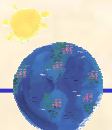
- Final clearance and publication - May 2004
- Recommends Performance Standards which are used to evaluate acceptability of similar test methods
- *Federal Register* (Vol. 69, No. 104, pp. 30693-4, 05/28/04)
  - Availability announced
- <http://iccvam.niehs.nih.gov>



# OECD Test Guidelines Program (1)

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- **Draft OECD TG 435 - *In Vitro* Membrane Barrier Test Method for Skin Corrosion**
  - Based on the validated and accepted Corrositex® test method protocol
  - Submitted by ICCVAM to OECD in February, 2003
    - First OECD TG to incorporate performance standards
    - Only in vitro TG that can classify all corrosivity packing groups
  - Circulated by OECD to National Coordinators (NC) for member country comments on May 21, 2004; emphasis on the issue of performance standards in OECD test guidelines
  - ICCVAM comments provided to OECD via the US NC on July 20, 2004
  - Adoption as TG possible in 2005

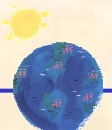




# OECD Test Guidelines Program (2)

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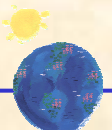
- **OECD GLP Working Group Task Force on *In Vitro* Studies**
  - Charged with developing international guidance on application of GLPs to *in vitro* toxicity testing
  - Task Force meeting in February, 2004
    - Advisory document finalized
    - Approved by the GLP WG in May 2004
    - Approval pending by OECD Joint Meeting, November, 2004
  - U.S. GLP Working Group members
    - James McCormack, FDA
    - Francis Liem, EPA



# OECD Test Guidelines Program (3)

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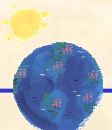
- **Draft OECD TG 434: Acute Dermal Toxicity - Fixed Dose Procedure**
  - Draft circulated from OECD on May 14, 2004
  - ICCVAM comments submitted to NC on July 20, 2004
- **Draft OECD TG 433: Acute Inhalation Toxicity - Fixed Concentration Procedure**
  - Draft circulated from OECD on June 9, 2004
  - ICCVAM comments submitted to NC on August 2, 2004



# OECD Test Guidelines Program (4)

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- **OECD Non-Animal Testing Validation Management Group for the Task Force on Endocrine Disruptors Testing and Assessment**
  - Functions to provide advice and coordination for related international validation studies
  - 2nd meeting in Paris, November 4-5, 2005
  - One NICEATM/ICCVAM representative nominated as member of the U.S. delegation



# ICCVAM-NICEATM Collaborations with ECVAM (1)

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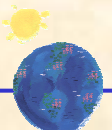
- ***ECVAM in vitro* dermal irritation validation study**
  - **ICCVAM and NICEATM observers on study management team**
    - Comments provided on test method protocols, chemical selection, etc.
  - **NICEATM/ICCVAM contributions**
    - **Identified Candidate Reference Chemicals**
      - ✓ Collaboration with EPA to review 2400 chemicals in the TSCATS database
    - **Estimated under-prediction rates for the rabbit skin test**
      - ✓ For current and GHS hazard classification categories



# ICCVAM-NICEATM Collaborations with ECVAM (2)

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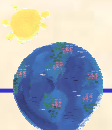
- **ICCVAM-NICEATM-ECVAM Workshop: *Validation Principles and Approaches for Toxicogenomic-based Methods***
  - December 2003, Ispra, Italy
  - Co-chaired by Len Schechtman( FDA, ICCVAM) and Raffaella Corvi (ECVAM)
  - Report and recommendations to be presented at the next SACATM meeting
  
- ***Workshop on Strategies to Replace In Vivo Acute Systemic Toxicity Testing***
  - September 2003, Ispra, Italy
  - Participation by 4 SACATM and ICCVAM members
  - Workshop report in press
  - Report and recommendations to be presented at the next SACATM meeting



# ICCVAM-NICEATM Collaborations with ECVAM (3)

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- Joint validation study on *in vitro* methods for acute toxicity
  - Final Phase underway; laboratory testing to be completed by December, 2004
  - Review anticipated in 2005



# **ICCVAM-NICEATM Collaborations with ECVAM (4)**

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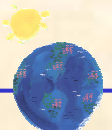
- **Collaborative Evaluation of Ocular Irritation Assays**
  - **Work-sharing: Background Review Document preparation**
  - **Coordinated expert panel reviews**
  - **Liaisons**
    - **ICCVAM Ocular Toxicity Working Group**
    - **ECVAM Ocular Irritation Task Force**



# ICCVAM-NICEATM: Other Related Activities

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- **Genomics and Alternatives to Animal Use 2004**
  - EHP mini-monograph in progress
- **Participation in upcoming scientific meetings**
  - **Society of Toxicology Annual Meeting, March, 2005**
  - **5th World Congress on Alternatives & Animal Use in the Life Sciences, August 2005**
    - Co-sponsors include NIH, NIEHS





# ICCVAM Agency Representatives\*

ATSDR	William Cibulas 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 Atin Datta, ORA
CPSC	Marilyn Wind (Vice-chair) Kailash Gupta Patricia Bittner Kristina Hatlelid	NCI	Alan Poland Marjorie Strobel
USDA	Jodie Kulpa-Eddy Elizabeth Goldentyer	NIEHS	William Stokes John Bucher Rajendra Chhabra Jerrold Heindel
DOD	Robert E. Foster Patty Decot Harry Salem John Frazier	NIOSH	Paul Nicolaysen Murali Rao
DOE	Marvin Frazier Marvin Stodolsky	NIH	Margaret Snyder Nelson Garnett
DOI	Barnett Rattner Sarah Gerould	NLM	Vera Hudson Jeanne Goshorn
DOT	George Cushmac Steve Hwang	OSHA	Surrender Ahir
EPA	Joseph Merenda, OSCP Karen Hamernik, OSCP Harold Zenick, ORD Angela Auletta, OPPT Suzanne McMaster, ORD Maurice Zeeman, OPPT Amy Rispin, OPP Deborah McCall, OPP		

\* As of October 2004



# NICEATM Staff

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## NIEHS

**William S. Stokes, D.V.M.**

**Director; Project Officer**

**Debbie McCarley**

**Special Assistant; Asst. Project Officer**

## Center Support Contract (ILS, Inc.)

**Ray Tice, Ph.D.**

**Principal Investigator**

**Brad Blackard, M.S.P.H.**

**Project Manager**

**Sue Brenzel**

**Webmaster**

**Neepa Choksi, Ph.D.**

**Toxicologist**

**Christina Inhof, M.S.P.H.**

**Sr. Project Coordinator**

**Linda Litchfield**

**Administrative Asst./Meeting Planner**

**Judy Strickland<sup>1</sup>, Ph.D.**

**Sr. Toxicologist**

**Michael Paris<sup>1</sup>**

**Sr. Project Coordinator**

**David Allen<sup>1</sup>, Ph.D.**

**Toxicologist**

**Jim Truax<sup>1</sup>**

**Project Coordinator**

**<sup>1</sup>Contract Option Staffing**

