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NIH William H. Natcher Conference Center
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Welcome to NIH:
The Nation’s Biomedical Research Agency

- **Mission:** Science in the pursuit of fundamental knowledge about the nature and behavior of living systems, and the application of that knowledge to extend healthy life and to reduce the burdens of illness and disability

- **27 Institutes and Centers**

- **31.2 $ Billion Budget (FY10)**
  - 83% awarded in 50,000 grants
  - 3,000 universities, medical schools, international research organizations
    - All 50 states and 90 countries
What is NICEATM?

- **The National Toxicology Program (NTP)**
  - Interagency Center for the Evaluation of Alternative Toxicological Methods

- A Center of the U.S. NTP, headquartered at the National Institute of Environmental Health Sciences, NIH, DHHS
  - NIEHS is one of the 27 NIH Institutes and Centers
  - NIEHS is headquarters for the NTP, which coordinates toxicology testing programs across the federal government
  - Located in Research Triangle Park, North Carolina

- Administers and provides scientific support for the **Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)**

- Conducts international validation studies
What is ICCVAM?

- The Interagency Coordinating Committee on the Validation of Alternative Methods was established by the NIEHS in 1997.
- Members represent the heads of 15 U.S. Federal regulatory and research agencies.
- Duties include:
  - Advising on test method development and validation
  - Conducting technical reviews of new safety testing methods
  - Transmitting formal recommendations to Federal agencies
  - Promoting regulatory acceptance of valid methods
  - Fostering national and international harmonization
- Began as ad hoc committee, 1994
- Standing committee, 1997
  - Permanent committee under NICEATM
The 15 ICCVAM Member Agencies

**Regulatory Agencies (7)**
- Consumer Product Safety Commission
- Department of Agriculture\(^1\)
- Department of the Interior\(^1\)
- Department of Transportation
- Environmental Protection Agency\(^1\)
- Food and Drug Administration\(^1\)
- Occupational Safety and Health Administration

**Research Agencies (8)**
- Agency for Toxic Substances and Disease Registry
- National Institute for Occupational Safety and Health-CDC
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy

\(^1\) Also has research component
ICCVAM’s Mission

- To facilitate and promote development, validation and regulatory acceptance of new and revised regulatory test methods that
  - Reduce, refine, and replace the use of animals in testing
  - Maintain and promote scientific quality and the protection of human health, animal health, and the environment

- Critical role in translating science from the bench to public health practice

- Together with NICEATM, provides the translation infrastructure for validation, evaluation, and regulatory acceptance

1Adopted by ICCVAM February 2004. All of ICCVAM’s activities are grounded in the U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. [Link](http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples)
NICEATM and ICCVAM Progress

- 37 alternative safety testing methods accepted/endorsed by U.S. regulatory agencies since 1999
- Recommendations for R&D, translation, and validation activities to further advance methods
- International guidances
  - Five new or updated test guidelines for ocular safety and allergic contact dermatitis testing adopted by OECD 2009-2010
- International partnerships:
  - International Cooperation on Alternative Methods (ICATM): Japan, Europe, Canada, and Korea
Areas of Emphasis:

- Priority test method activities with the greatest 3Rs impact
  - Acute toxicity testing
  - Allergic contact dermatitis testing
  - Biologics testing
  - Ocular safety testing
- Application of new science and technology
- Partnerships
- International cooperation

1Available at http://iccvam.niehs.nih.gov/docs/5yearplan.htm
Why are Eye Safety Testing and Eye Hazard Labeling Important? (1)

- Each year, approximately 2 million eye injuries occur in the U.S.\(^1\)
  - Of these, more than 40,000 result in permanent visual impairment
- Household cleaning chemicals and other chemical products are the leading cause of consumer product-related eye injuries in children under age 10\(^2\)

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\(^1\) Based on CPSC National Electronic Injury Surveillance Survey (CPSC-NEISS) data collected from 100 Emergency Departments

\(^2\) Chemicals exceeded only by Hardware/Tools/Construction (28%) and Sports (14%)

Why are Eye Safety Testing and Eye Hazard Labeling Important? (2)

- Labels provide safety messages to help prevent injuries
  - Informs consumers and workers about the potential for eye injuries from the product
  - Provides instructions on how to avoid exposures
  - Provides first aid instructions in case of accidental exposure

- U.S. agencies requiring testing and/or labeling for eye hazards:
  - Environmental Protection Agency
  - Consumer Product Safety Commission
  - Occupational Safety and Health Administration
  - Food and Drug Administration
Why Seek Alternatives to the Rabbit Eye Test?

- **Replacement (some testing situations):** Available and approved/recommended non-animal test methods
  - Bovine corneal opacity and permeability (BCOP)
  - Cytosensor® Microphysiometer (CM)
  - Isolated chicken eye (ICE)

- **Refinement:** Pain management procedures that should *always* be used when it is determined necessary to conduct the rabbit eye test

- **Reduction:** Strategies to minimize numbers
  - 1990: 6 animals per test; no *in vitro* test methods
  - 2011: 0-3 animals; 3 *in vitro* test methods
Ocular Toxicity Scientific Symposia (1)

Symposium I: Mechanisms of Chemically-Induced Ocular Injury and Recovery (May 11-12, 2005)

National Institutes of Health - Bethesda, MD

Sponsored by ICCVAM, NICEATM, ECVAM and COLIPA: the European Cosmetic, Toiletry and Perfumery Association

Goals

- Identify research needed to address current knowledge gaps for alternative test methods
- Advance the development and validation of ocular toxicity test methods for regulatory testing that provide for protection of human health while reducing, refining (less pain and distress), and/or replacing the use of animals
Symposium II: Minimizing Pain and Distress in Ocular Toxicity Testing (May 13, 2005)

National Institutes of Health - Bethesda, MD

Sponsored by ICCVAM, NICEATM, ECVAM and the European Cosmetic, Toiletry and Perfumery Association

- **Goals**
  - Identify research needed to address current knowledge gaps
  - Advance the development and validation of ocular toxicity test methods for regulatory testing that provide for protection of human health while reducing, refining (less pain and distress), and/or replacing the use of animals

- 2005 Peer Review Panel Meeting
  - January 11-12, 2005
  - Open to the public
  - Panel of 24 scientists, 6 countries

- Evaluated four alternative test methods for identifying severe irritants and corrosives
  - BCOP
  - HET-CAM
  - ICE
  - IRE

- ICCVAM evaluation report and recommendations published November 2006

- ICCVAM recommendations were accepted by Federal agencies, and positive results in these test methods (i.e., BCOP and ICE) may now be used for certain regulatory testing purpose

- 2009 Peer Review Panel Meeting
  - May 19-21, 2009
  - Open to the public
  - Panel of 22 scientists, 6 countries

- Evaluated 10 alternative test methods and strategies
  - Routine use of analgesics, topical anesthetics, and humane endpoints
  - Low Volume Eye Test
  - *In vitro* test methods and strategies

- ICCVAM evaluation report and recommendations published September 2010

- Federal agency responses due to ICCVAM March 7, 2011
  - Many available now
Developing Future Test Methods: High Throughput *In Vitro* Screening

- NIH (NIEHS and NHGRI), EPA, and FDA collaborating to use the NIH Chemical Genomics Center: “Tox 21”
  - Robotic quantitative high-throughput *in vitro* screening (HTS)
  - ToxCast™: 600 assays

- Using 10,000 chemicals to identify toxicity pathways

- NICEATM-ICCVAM
  - >900 ICCVAM reference chemicals nominated for inclusion
  - Ocular safety testing data for many of these reference substances
  - ICCVAM considers and nominates *in vitro* assays for HTS
  - Expect *in vitro* test methods incorporating pathway-based biomarkers to emerge for safety testing
Developing Future Test Methods: NIH-FDA Regulatory Science Program

- Interagency partnership between National Institutes of Health and the U. S. Food and Drug Administration (FDA) to foster regulatory science
- Specialized and inter-disciplinary area of biomedical research that serves to generate new knowledge and tools for assessing experimental therapies, preventives, and diagnostics
- Accelerate development and use of new tools, standards and approaches to efficiently develop products and to more effectively evaluate product safety, efficacy and quality
- Four grants announced September 27, 2010
  - $9.34M US awarded over 3 years
  - Co-funded by NIH Common Fund and U.S. FDA
  - One grant to support an in vitro test battery for eye injury assessment (MB Research Labs)
    • See poster at this workshop

http://commonfund.nih.gov/regulatoryscience/
Integrating New Science Technologies

Integrated Strategies: Potential Sources of Data and Information

**Integrated Ocular Safety Assessment**

- **In Vitro Data/HTS** “Tox 21”
- **Physicochemical Properties**
- **Toxicogenomic Data**
- **Structural Alerts/QSAR**
- **Test Results for Similar Substances**
- **Other Computational Models**
- **Human Data**
  - Accidental exposures
  - Ethical studies
- **Animal Toxicity Data**

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