



## NICEATM and ICCVAM: Recent ICATM Contributions and Future Plans

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ICCVAM Chair, 2007-2010

U.S. Consumer Product Safety Commission (Retired)

ICATM: Translating Science to Provide Improved Public  
Health Safety Assessment Tools

Society of Toxicology

50<sup>th</sup> Anniversary Annual Meeting

March 7, 2011

Washington, DC



National  
Toxicology  
Program



NIHS



# 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
- ICCVAM Authorization Act of 2000
  - Permanent committee under NICEATM



ICCVAM  
NICEATM



# 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
  - NTP 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



# The 15 ICCVAM Member Agencies

## Regulatory Agencies (7)

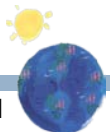
- Consumer Product Safety Commission
- Department of Agriculture<sup>1</sup>
- Department of the Interior<sup>1</sup>
- Department of Transportation
- Environmental Protection Agency<sup>1</sup>
- Food and Drug Administration<sup>1</sup>
- Occupational Safety and Health Administration

## 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

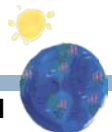
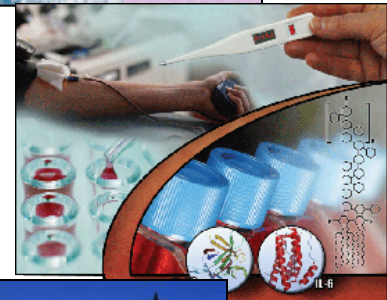
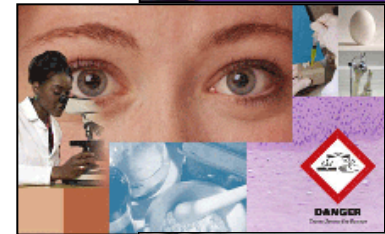
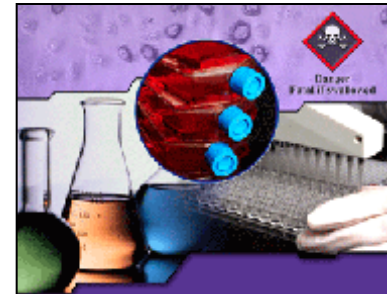


<sup>1</sup> Also has research component



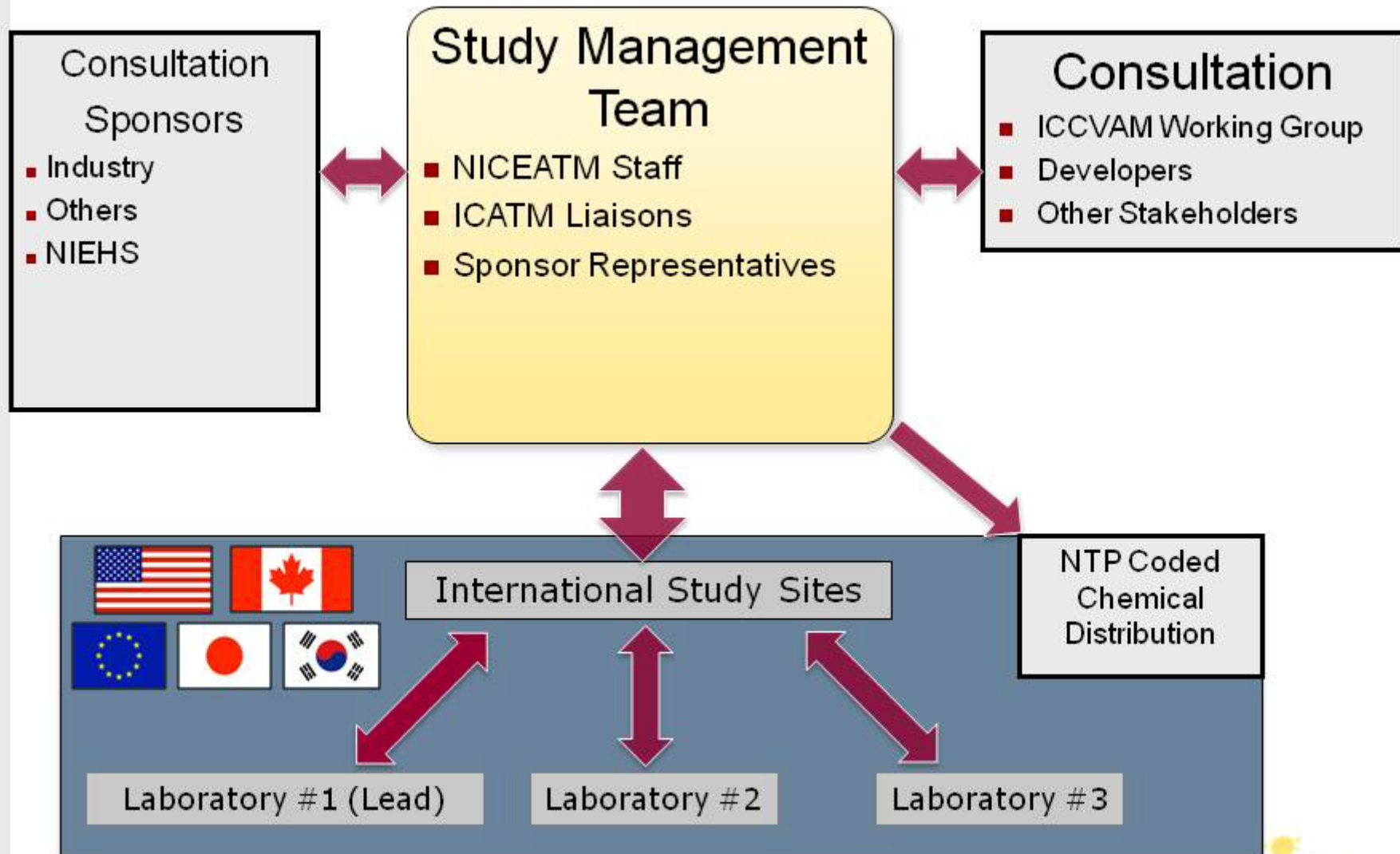
# NICEATM and ICCVAM Progress

- 40 alternative safety testing methods accepted/endorsed by U.S. and international agencies since 1999
  - Can significantly reduction, refinement, and replacement of animal use
  - International test guidelines and guidances
- Recommendations for R&D, translation, and validation activities to further advance methods





# NICEATM Coordination: International Validation Studies



# ICCVAM Test Method Evaluations: Coordination with ICATM Partners

## Interagency Test Method Working Group (WG)

- ICATM partners designate a liaison to WG
- ICATM input to draft Background Review Documents, draft test method recommendations

## Independent Scientific Peer Review

- ICATM and public: nominations for international Peer Review Panel members
- ICATM partners help solicit public comments on draft BRDs/recommendations
- ICATM attendance at public Panel meeting
- ICATM and public availability of Final Panel report

## Harmonized Test Method Recommendations

- WG& ICATM liaisons consider PRP Report, SACATM and public comments
  - Propose final recommendations
  - Seek ICATM consensus on recommendations (or document basis for differences)
- ICCVAM Final Reports
  - Forwarded to regulatory authorities for acceptance decisions
  - Provided to ICATM partners to send to their regulatory authorities
  - Forwarded for international test guideline adoption (OECD, etc.)

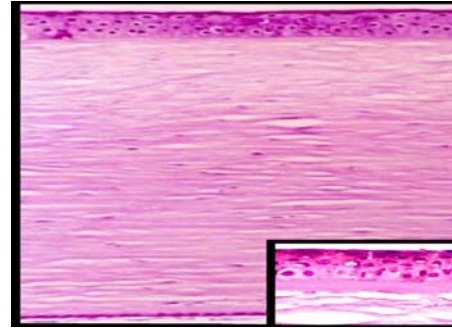


# Recently Adopted Alternatives: Isolated Chicken Eye (ICE) Test Method

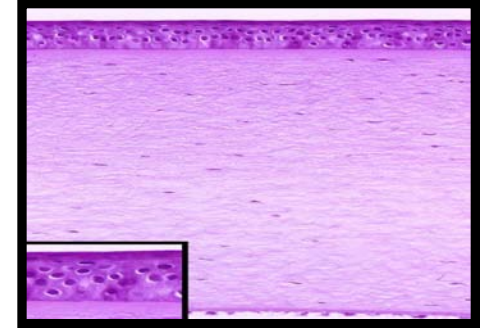
- Whole eyes isolated from chickens:

- Easy to collect
- Similar to human
- Bowman's layer present
- Very uniform

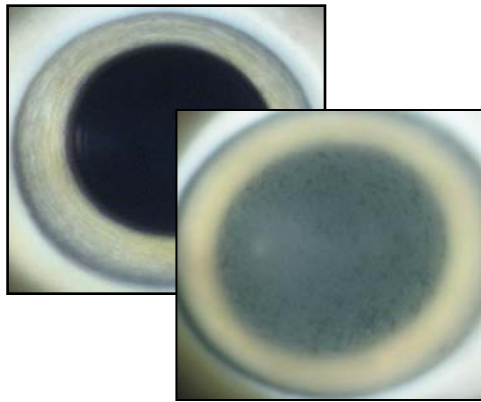
Human



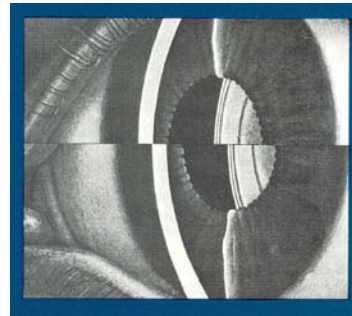
Chicken



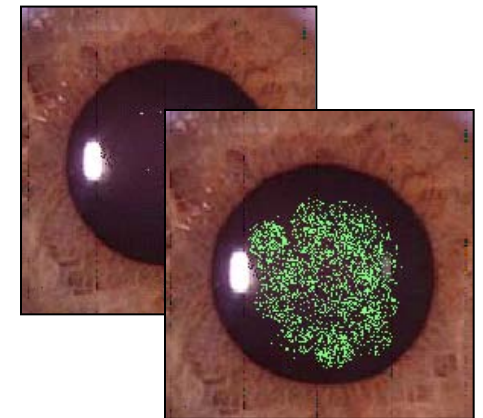
- **3 primary endpoints** –combined for an *in vitro* hazard category



Corneal Opacity

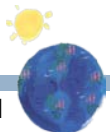


Corneal Swelling



Fluorescein Staining

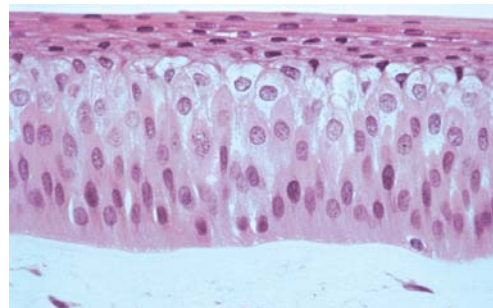
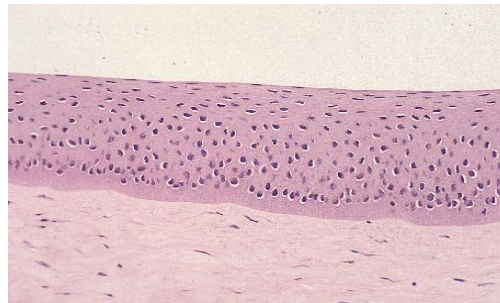
- ***ICE is now accepted internationally (OECD TG 438) as a screen for identifying ocular corrosives and severe irritants***



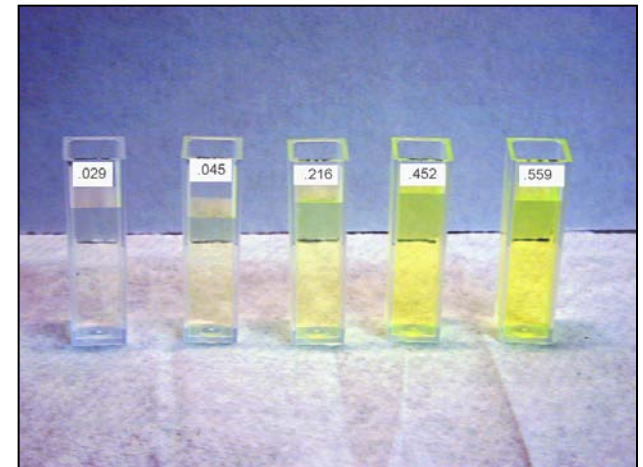


# Recently Adopted Alternatives: Bovine Corneal Opacity and Permeability (BCOP)

- Viable corneas maintained in organ culture
- Test substance exposure on the corneal surface
- Scores combined to calculate an in vitro irritancy score
- ***BCOP is now accepted internationally (OECD TG 438) as a screen for identifying ocular corrosives and severe irritants***

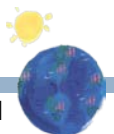


**Quantitative** change in light passage (opacity)



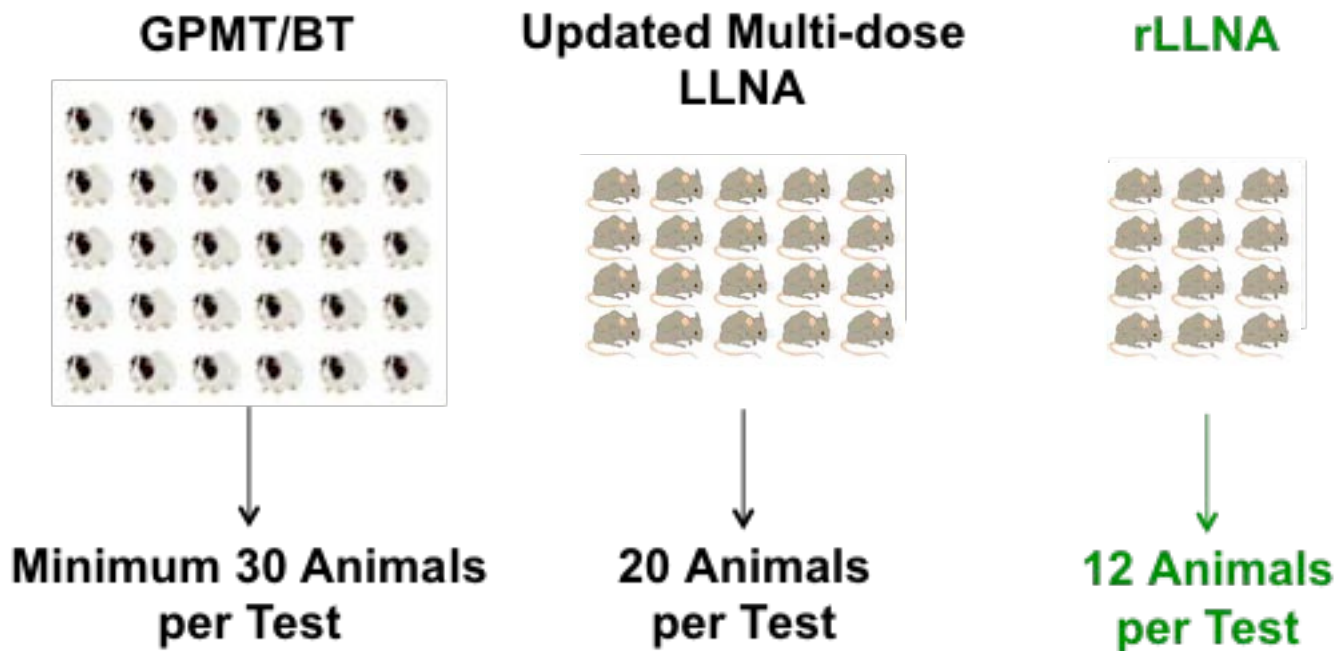
**Quantitative** change in the epithelial barrier (fluorescein penetration)

Photos from MB Research Laboratories (<http://www.mbresearch.com/bcop.htm>)

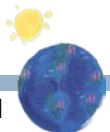


# Recent International Adoption: Reduced LLNA (rLLNA)

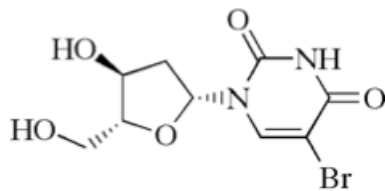
- Reduces animal use by 40% for each test vs. multi-dose LLNA
  - Modification of the murine local lymph node assay (LLNA) to test for allergic contact dermatitis hazards
  - Applicable to most testing situations
- OECD LLNA test guideline (TG 429) updated to include rLLNA in 2010



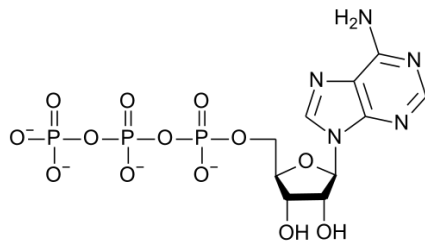
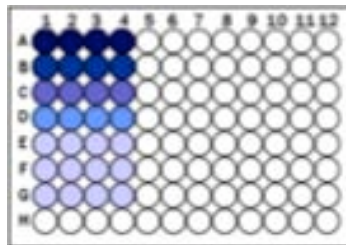
Abbreviations: GPMT/BT = guinea pig maximization test/Buehler test



# Recent International Adoption: Nonradioactive “Green” LLNA Test Methods



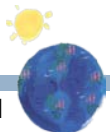
5-bromo-2'-deoxyuridine



Adenosine triphosphate

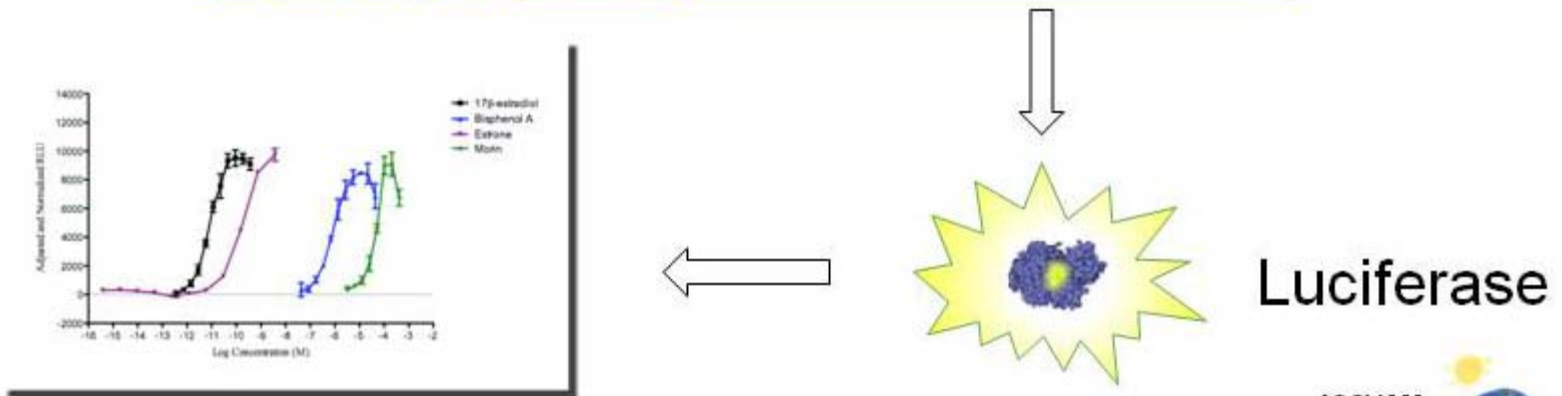
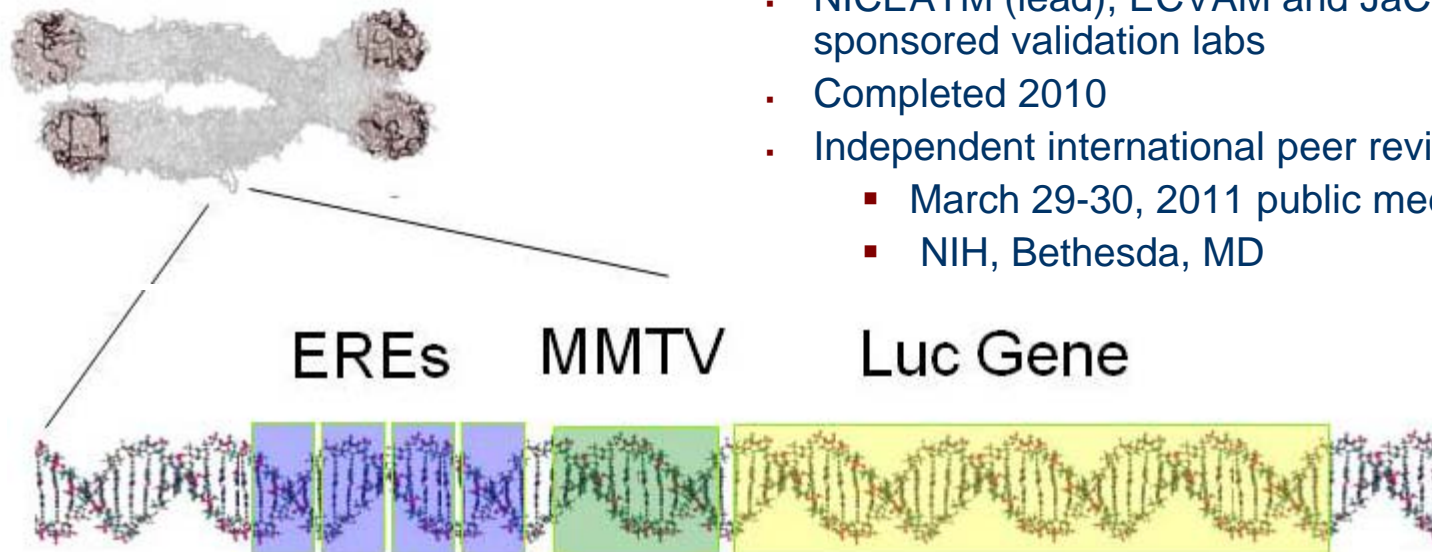


- LLNA: BrdU-ELISA
  - Measures BrdU incorporation as a correlate to lymph node cell proliferation
  - ELISA detects peroxidase-labeled BrdU antibody
- LLNA: DA
  - Measures ATP content as a correlate to lymph node cell proliferation
  - ATP content assessed by a luciferin-luciferase assay to measure ATP bioluminescence
- OECD Test Guidelines for each adopted in 2010
  - TG 442A - LLNA: DA
  - TG 442B - LLNA: BrdU-ELISA



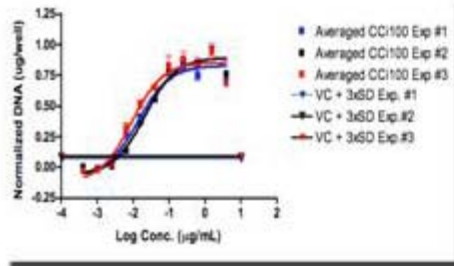
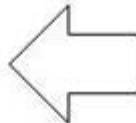
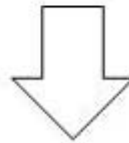
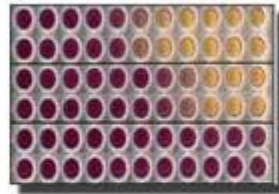
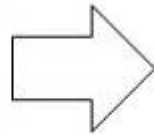
# International Validation Study: BG1 Luc ER TA (LumiCell<sup>®</sup>) Assay

- Human ovarian carcinoma cells (BG1)
- NIEHS SBIR-funded development (XDS, Inc)
- NICEATM (lead), ECVAM and JaCVAM sponsored validation labs
- Completed 2010
- Independent international peer review
  - March 29-30, 2011 public meeting
  - NIH, Bethesda, MD

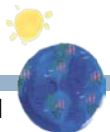




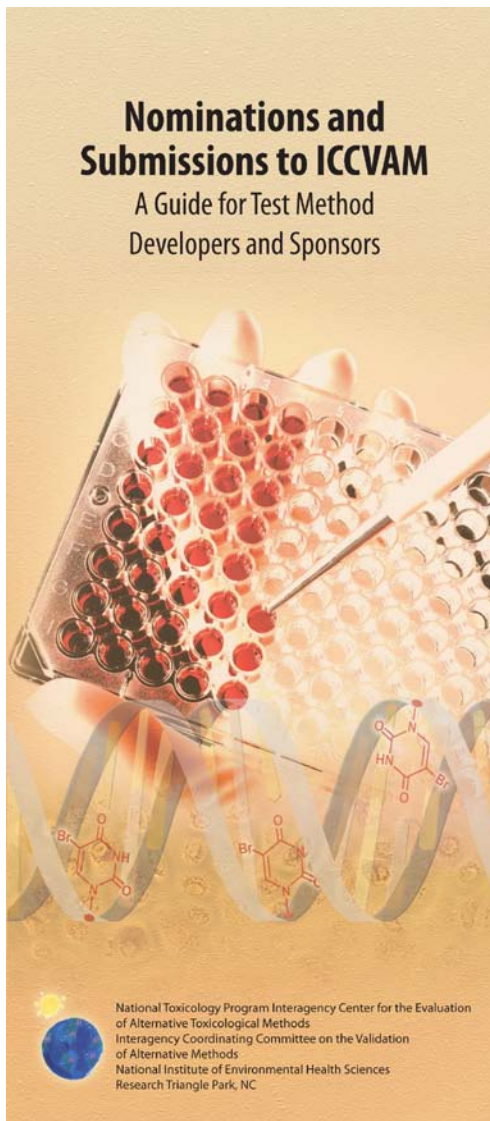
# International Validation Study: MCF-7 Cell Proliferation Assay



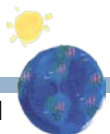
- Human breast carcinoma cells (MCF-7)
- Cell proliferation – DNA content
- NIEHS SBIR-funded development (Certichem, Inc.)
- NICEATM (lead), KoCVAM and JaCVAM sponsored validation labs
- Scheduled completion – Spring 2011



# Nominations and Submissions to ICCVAM



- Advances in science and technology are expected to yield new methods applicable to regulatory safety testing
  - Tox 21, ToxCast, etc.
- NICEATM and ICCVAM seek nominations and submissions for:
  - Validation studies
  - Formal evaluations
  - Other activities
- Of particular interest are methods with potential to:
  - Provide improved safety or hazard assessment
  - Reduce, refine, and replace the use of animals
- Contact NICEATM for more information



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Thank you for your attention.

NICEATM-ICCVAM

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