NICEATM

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

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM Workshop Series on Best Practices for Regulatory Safety Testing - Assessing the Potential for Chemically Induced Eye Injuries:

Introduction and Public Health Impact of Chemically Induced Eye Injuries

William S. Stokes, D.V.M., DACLAM
Rear Admiral, U.S. Public Health Service
Director, NICEATM
Executive Director, ICCVAM

January 19, 2011

NIH William H. Natcher Conference Center
Bethesda, Maryland

National Toxicology Program

NIEHS

National Institutes of Health

Department of Health & Human Services • USA

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 **N**ational Toxicology Program (NTP) **I**nteragency **C**enter for the **E**valuation of **A**lternative **T**oxicological **M**ethods
- 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

National Toxicology Program
NTP

What is ICCVAM?

- The **I**nteragency **C**oordinating **C**ommittee on the **V**alidation of **A**lternative **M**ethods 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

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

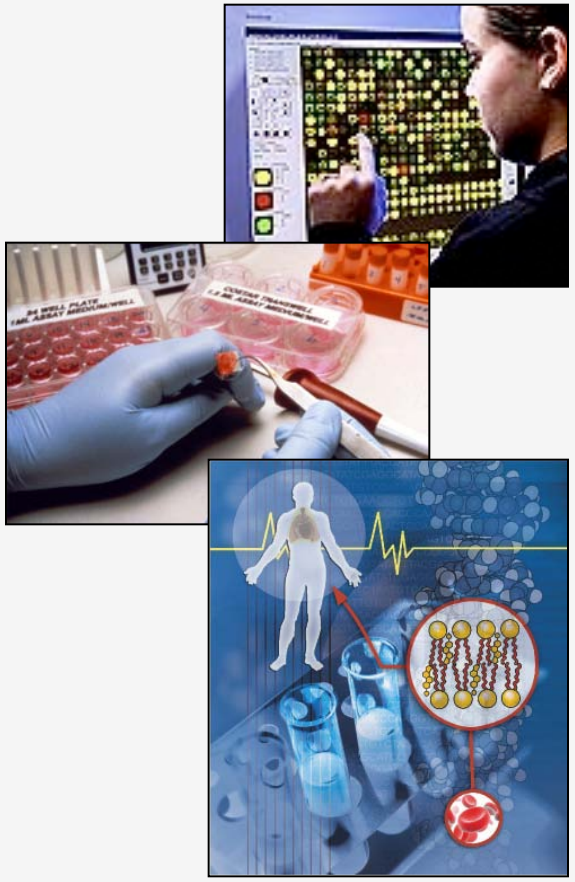
Research Agencies (8)

- 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[1]

- *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



[1]Adopted 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.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

NICEATM-ICCVAM Five-Year Plan[1]: 2008-2012

- 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

[1]Available 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]

[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%)

McGwin et al. (2006). J Safety Res. 37:501-506; McGwin et al. (2006). Inv Ophthalmol. & Vis Science; Cross et al. (2008). J AAPOS. 12:626-628.

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)

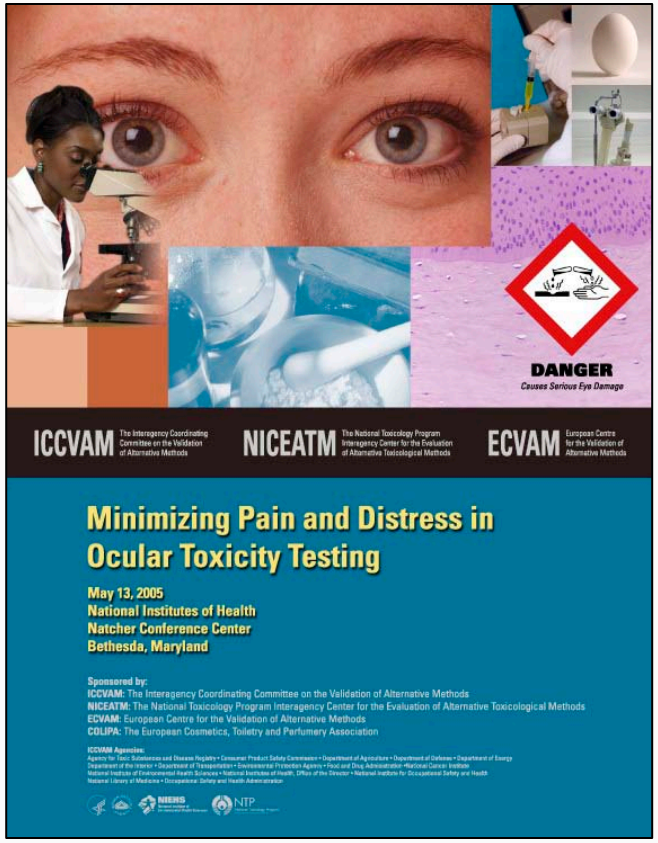
Symposium I: Mechanisms of Chemically-Induced Ocular Injury and Recovery (May 11-12, 2005)

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

Ocular Toxicity Scientific Symposia (2)



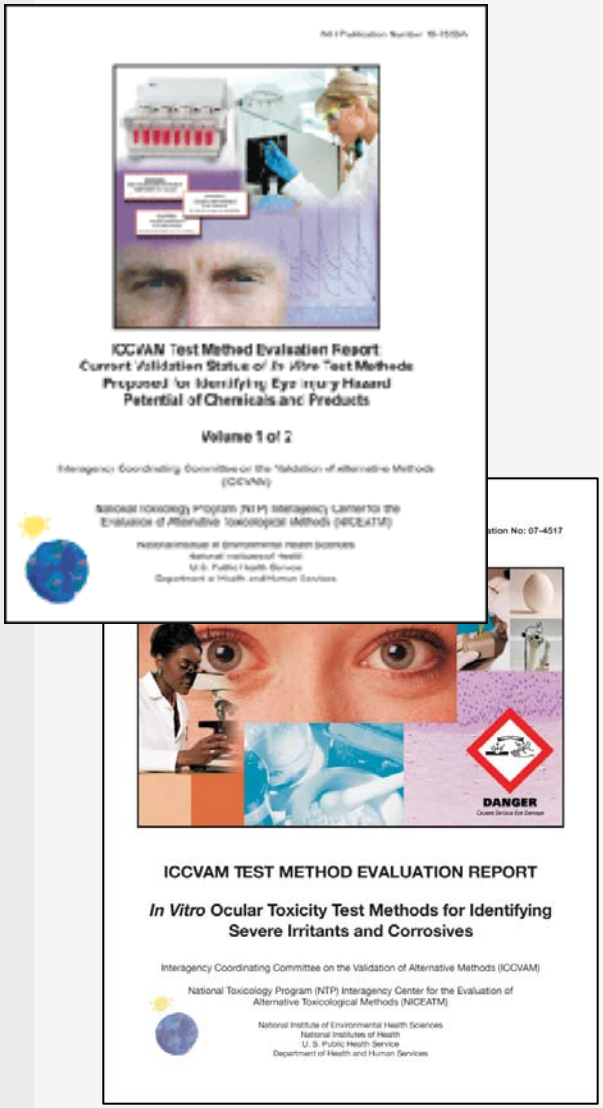
Symposium II: Minimizing Pain and Distress in Ocular Toxicity Testing (May 13, 2005)

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

ICCVAM Test Method Evaluation: Ocular Safety Testing (2005)

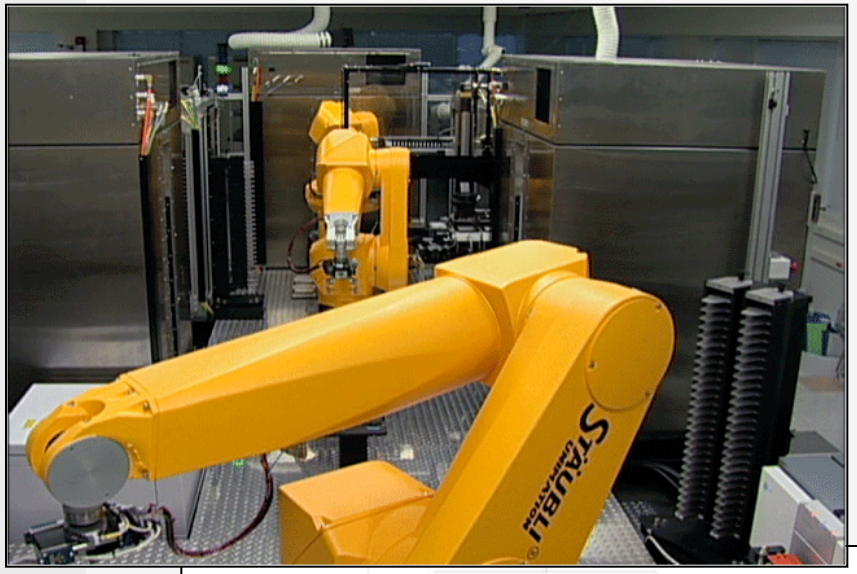


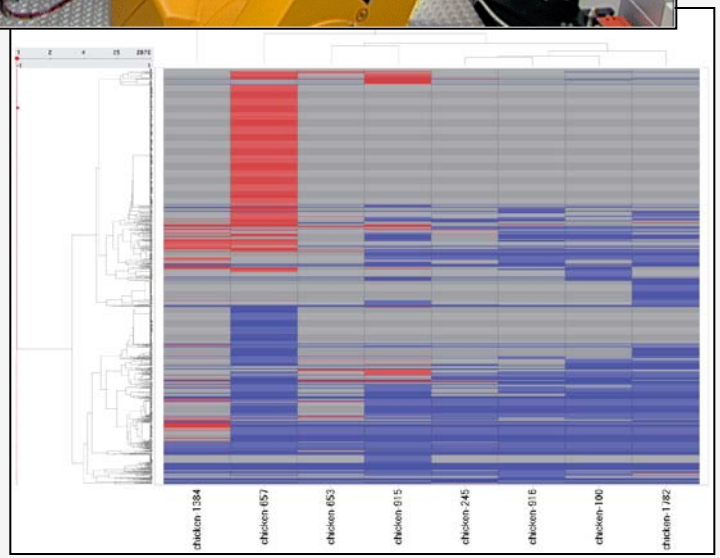
- 2005 Peer Review Panel Meeting
  - January 11-12, 2005
  - Open to the public
  - Panel of 24 scientists, 6 countries
- Evaluated four alternative test methods for identifying severe irritants and corrosives
  - BCOP
  - HET-CAM
  - ICE
  - IRE
- ICCVAM evaluation report and recommendations published 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

ICCVAM Test Method Evaluation: Ocular Safety Testing (2009)

- 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

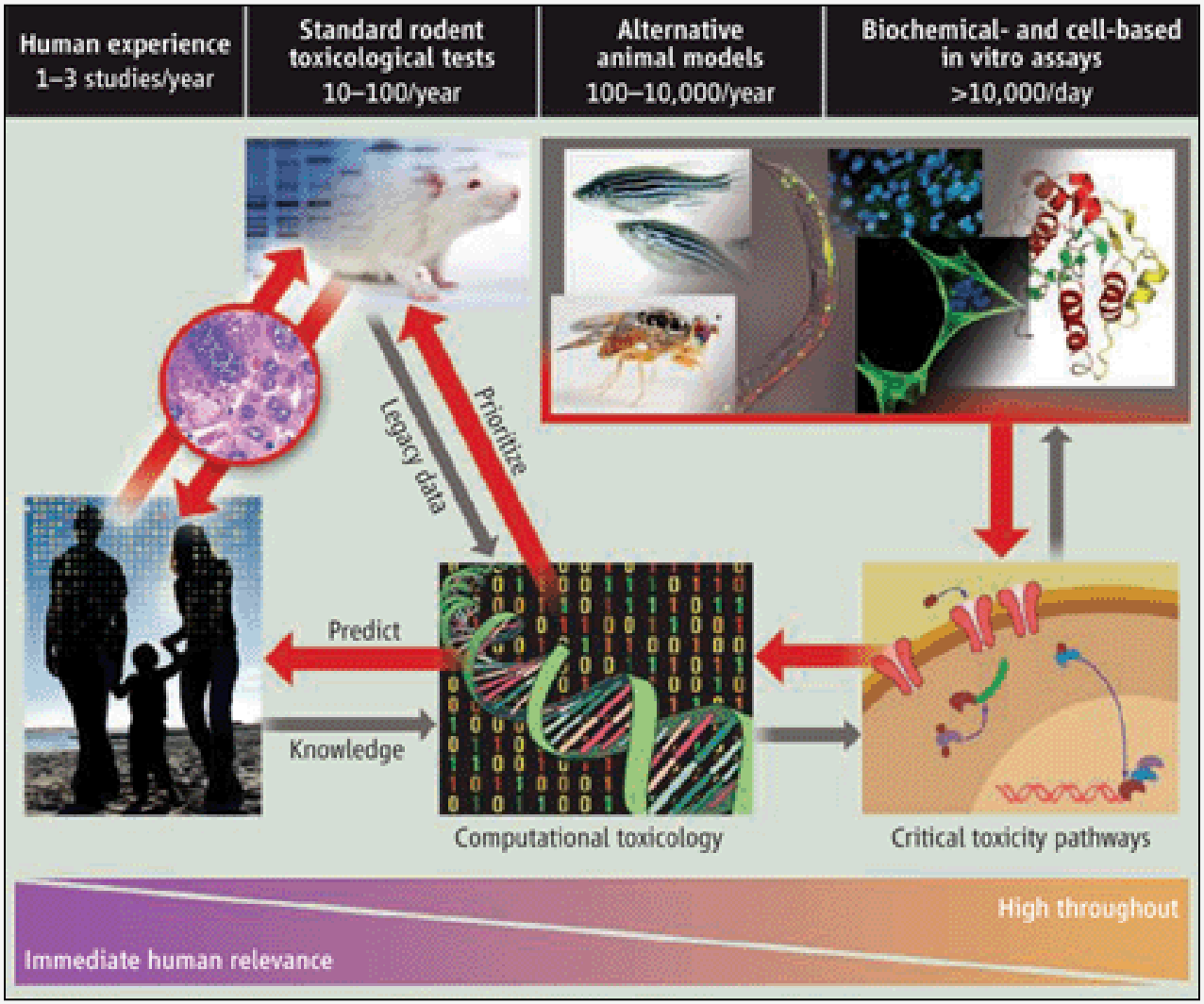
- Interagency partnership between National Institutes of Health and the U. S. Food and Drug Administration (FDA) to foster regulatory science
- Specialized and inter-disciplinary area of biomedical research that serves to generate new knowledge and tools for assessing experimental therapies, preventives, 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

Francis S. Collins, M.D., Ph.D.
NIH Director

Margaret Hamburg, M.D.
FDA Commissioner

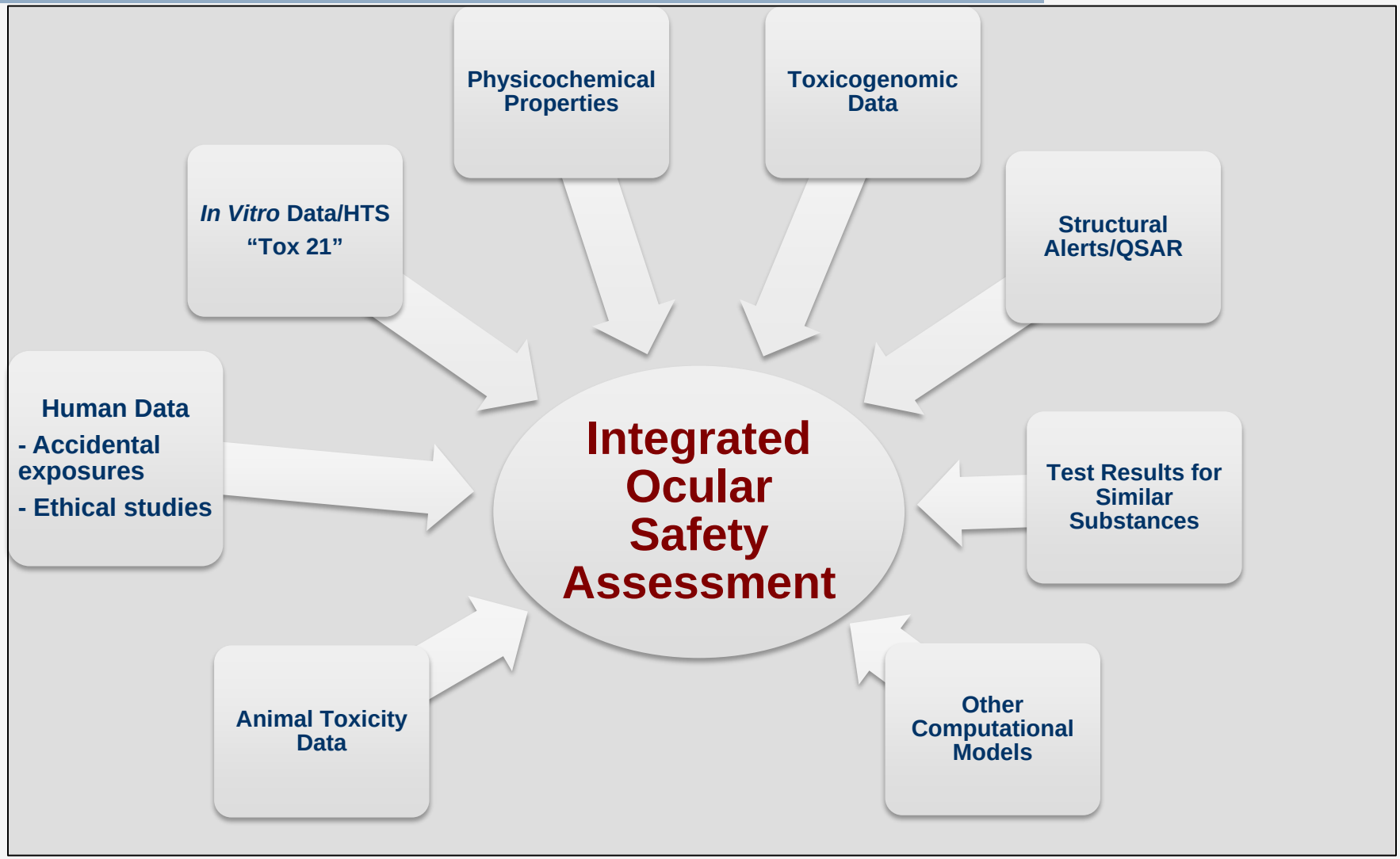
http://commonfund.nih.gov/regulatoryscience/

Integrating New Science Technologies



Collins FS, Gray GM, Bucher JR. 2008. Transforming Environmental Health Protection. Science 319:906-07

Integrated Strategies: Potential Sources of Data and Information



Source: Adapted from Stokes WS, Wind M. 2010. Validation of innovative technologies and strategies for regulatory safety assessment methods: challenges and opportunities. *ALTEX* 27:87-95.

Acknowledgements: ICCVAM Interagency Ocular Toxicity Working Group (OTWG)

Consumer Product Safety Commission
Marilyn Wind, Ph.D. (to July 2010)
Adrienne Layton, Ph.D.

Department of Defense
Harry Salem, Ph.D.

Department of Transportation
Steve Hwang, Ph.D.

Environmental Protection Agency
Office of Pesticide Programs
Jonathan Chen, Ph.D.
Masih Hashim, Ph.D., D.V.M.
Jonathan Chen, Ph.D.
John R. “Jack” Fowle III, Ph.D., DABT
Masih Hashim, D.V.M., Ph.D.
Karen Hicks
Marianne Lewis
Debbie McCall
Timothy McMahon, Ph.D.
Mark Perry
John Redden
Jenny Tao, Ph.D.
Office of Research and Development
Meta Bonner, Ph.D.
Andrew Geller, Ph.D.
Office of Science Coordination and Policy
Karen Hamernik, Ph.D.

Food and Drug Administration
Center for Drug Evaluation and Research
Paul Brown, Ph.D.
Wiley Chambers, M.D.
Abigail Jacobs, Ph.D.
Jill Merrill, Ph.D., DABT **(OTWG Chair)**
Center for Food Safety and Nutrition
Robert Bronaugh, Ph.D.
Donnie Lowther
Neil Wilcox, D.V.M., M.P.H.
Office of the Commissioner
Suzanne Fitzpatrick, Ph.D., DABT

National Institute of Environmental Health Sciences
Warrren Casey, Ph.D., DABT
Mark Cesta, D.V.M., DACVP
Raymond (Buck) Grissom, Ph.D.
William Stokes, D.V.M., DACLAM (Director, NICEATM)

Occupational Safety and Health Administration
Surender Ahir, Ph.D.

European Centre for the Validation of Alternative Methods – Liaison
João Barroso, Ph.D.
Valerie Zuang, Ph.D.

Japanese Center for the Validation of Alternative Methods – Liaison
Hajime Kojima, Ph.D.

Acknowledgements: ICCVAM Five-Year Plan Implementation Subcommittee

Agency for Toxic Substances and Disease Registry
Moiz Mumtaz, Ph.D.

Consumer Product Safety Commission
Marilyn Wind, Ph.D. (to July 2010)

Department of Agriculture
Jodie Kulpa-Eddy, D.V.M.

Food and Drug Administration
Office of Science
Suzanne Fitzpatrick, Ph.D., DABT
(Subcommittee Chair)
Center for Drug Evaluation and Research
Abigail Jacobs, Ph.D.
Center for Devices and Radiological Health
Vasant Malshet, Ph.D.
Center for Food Safety and Nutrition
David Hattan, Ph.D.

ICCVAM Research and Development Working Group

Agency for Toxic Substances and Disease Registry
Bruce Fowler, Ph.D.

Department of Defense
Leonard Smith, Ph.D.

Environmental Protection Agency
John (Jack) Fowle III, Ph.D., DABT

National Institute of Environmental Health Sciences
William Stokes, D.V.M., DACLAM
Debbie McCarley

National Institutes of Health
Margaret Snyder, Ph.D.

Food and Drug Administration
Center for Biologics Evaluation and Research
Richard McFarland, Ph.D., M.D.
National Center for Toxicological Research
Donna Mendrick, Ph.D.

National Cancer Institute
Myrtle Davis-Millin, D.V.M., Ph.D.

National Institute of Environmental Health Sciences
Warren Casey, Ph.D., DABT
Jerrold (Jerry) Heindel, Ph.D.

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

Agency for Toxic Substances and Disease Registry
Moiz Mumtaz, Ph.D.
Bruce Fowler, Ph.D.
Edward Murray, Ph.D.
Eric Sampson, Ph.D.

Consumer Product Safety Commission
Joanna Matheson, Ph.D.,
Kristina Hatlelid, Ph.D.

Department of Agriculture
Jodie Kulpa-Eddy, D.V.M. **(Acting *Chair*)**
Elizabeth Goldentyer, D.V.M.

Department of Defense
David Honey, Ph.D.
Patty Decot
Terry Besch, DVM, DACLAM, DACVPM

Department of Energy
Michael Kuperberg, Ph.D.
Marvin Stodolsky, Ph.D.

Department of the Interior
Barnett A. Rattner, Ph.D.

Department of Transportation
George Cushmac, Ph.D.
Steve Hwang, Ph.D.

Principal Agency Representative
Alternate Principal Agency Representative

Environmental Protection Agency
Office of Pesticide Programs
John R. Fowle III, Ph.D., DABT
Vicki Dellarco, Ph.D.
Tina Levine, Ph.D.
Deborah McCall
OECD Test Guidelines Program
Christine Augustyniak, Ph.D.

National Cancer Institute
T. Kevin Howcroft, Ph.D.
Chand Khanna, D.V.M., Ph.D.

National Institute for Occupational Safety and Health
Paul Nicolaysen, V.M.D.

National Institute of Environmental Health Sciences
William S. Stokes, D.V.M., DACLAM
Warren Casey, Ph.D., DABT
Rajendra S. Chhabra, Ph.D., DABT
Jerrold J. Heindel, Ph.D.

National Institutes of Health
Margaret D. Snyder, Ph.D.

National Library of Medicine
Pertti Hakkinen, Ph.D.
Jeanne Goshorn, M.S.

Occupational Safety and Health Administration
Surender Ahir, Ph.D.

Food and Drug Administration
Office of the Commissioner
Suzanne Fitzpatrick, Ph.D., DABT
Center for Biologics Evaluation and Research
Richard McFarland, Ph.D., M.D.
Ying Huang, Ph.D.
Center for Drug Evaluation and Research
Abigail C. Jacobs, Ph.D.
Paul C. Brown, Ph.D.
Center for Devices and Radiological Health
Vasant Malshet, Ph.D., DABT
Center for Food Safety and Nutrition
David G. Hattan, Ph.D.
Neil L. Wilcox, D.V.M., M.P.H.
Center for Veterinary Medicine
Devaraya Jagannath, Ph.D.
M. Cecilia Aguila, D.V.M.
National Center for Toxicological Research
Paul Howard, Ph.D.
Donna Mendrick, Ph.D.
Office of Regulatory Affairs
Laurence A. D'Hoostelaere, Ph.D.

Acknowledgements: NICEATM

National Institute of Environmental Health Sciences

William S. Stokes, D.V.M., DACLAM	*Director*
Warren Casey, Ph.D., DABT	*Deputy Director*
Debbie McCarley	*Special Assistant*

Center Support Contract (ILS, Inc.)

David Allen, Ph.D., *Principal Investigator*
Steven Morefield, M.D., *Project Manager*
Elizabeth Lipscomb, Ph.D.
James Truax, M.A.
Linda Litchfield
Anna Lee Mosley
Catherine Sprankle
Linda Wilson

Thank you for your attention.

Questions?

Dr. William Stokes
stokes@niehs.nih.gov

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

The USPHS Commissioned Corps:
Protecting, Promoting, and Advancing the Health and Safety of the Nation