NICEATM

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

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST): State of the Science and the Path Forward

Welcoming Remarks and Introduction

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November 28, 2012
William H. Natcher Conference Center
Bethesda, MD

National Toxicology Program
U.S. Department of Health and Human Services

What is NICEATM?

- The **N**ational Toxicology Program (NTP) **I**nteragency **C**enter for the **E**valuation of **A**lternative **T**oxicological **M**ethods: "***Nigh' see tum"***

- A Center of the NIEHS and NTP
  - NIEHS: one of 27 NIH Institutes and Centers
  - NTP headquartered at the National Institute of Environmental Health Sciences, NIH, DHHS
    - conducts and coordinates toxicology testing programs across the federal government
  - Research Triangle Park, North Carolina, USA

- NICEATM functions:
  - Conduct international validation studies
  - Administer and provide scientific support for the **Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)**
    - Evaluate proposed new, revised, and alternative test methods

National Toxicology Program
NTP

What is ICCVAM?

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

- Established by NIEHS in 1997
  - In response to Public Law 103-43
- ICCVAM Authorization Act of 2000
  - ICCVAM becomes permanent committee under NICEATM
- Members: 15 U.S. Federal regulatory and research agencies
- **Purposes and duties include**:
  - Reduce, replace, and refine animal use in testing
  - Share experiences between agencies, avoid duplication of effort
  - Advise on test method development and validation
  - Ensure test methods are validated to meet agency needs
  - Conduct technical reviews of new testing methods
  - Transmit recommendations to Federal agencies for adoption decisions
  - Foster national and international harmonization

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-CDC
- 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

Other agencies as appropriate

[1] Also has research component

NICEATM and ICCVAM Progress

- 63 alternative safety testing methods accepted/endorsed by U.S. and international authorities since 1999[1]
- Recommendations for R&D, translation, and validation activities to further advance methods
- International test guidelines and guidances
- International Cooperation on Alternative Methods (ICATM):
  - Japan: JaCVAM, NIHS
  - Europe: EURL ECVAM, IHCP
  - Canada: Health Canada
  - Korea: KoCVAM, KFDA

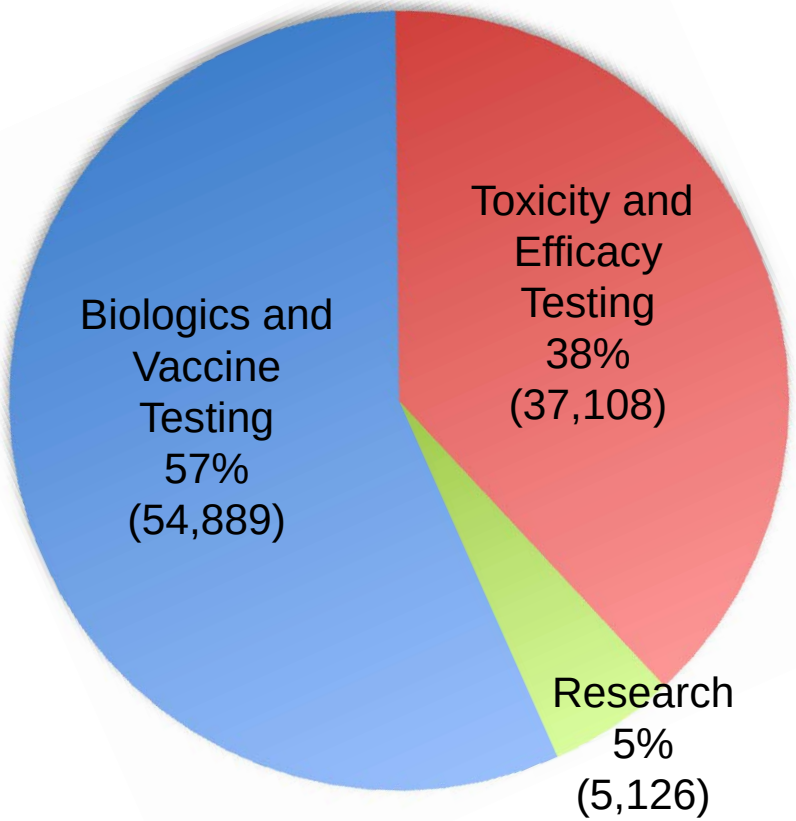
[1] U.S. and international acceptance of alternative methods, 1998-2012. Website: http://iccvam.niehs.nih.gov/about/accept.htm

NICEATM-ICCVAM Five-Year Plan: 2008-2012

- Vaccine Potency and Safety Testing
  - One of ICCVAM's four highest priorities:
    - Large numbers of animals required
    - Involves significant unrelieved pain and distress
    - Multiple agencies involved
- "NICEATM and ICCVAM will:
  - Evaluate alternative test methods and testing strategies for vaccine potency testing
  - Facilitate acceptance of adequately validated test methods and humane endpoints found to be sufficiently accurate and reliable."

Use of Animals for Testing that Involves Unrelieved Pain and Distress (No Pain Relievers Used)

Animals by Testing Type Reported to USDA (2010):



- 57% (54,889) of the animals reported to USDA that experience unrelieved pain and distress are used for testing Biologics and Vaccines
- Including rats, mice, and birds (not reported to USDA):
  - Est. 2 million animals used for testing that involves unrelieved pain and distress (in the U.S.)

Data for all states with all animal data for Column E of APHIS Form 7023; USDA. 2010. Annual Report - Animal Usage by Fiscal Year. United States Department of Agriculture. Animal and Plant Health Inspection Service. Available at: http://www.aphis.usda.gov/animal_welfare/efoia/7023.shtml

NICEATM-ICCVAM International Workshop: Human and Veterinary Vaccine Potency and Safety Testing

- September 14-16, 2010 – Co-organizers included:
  - ECVAM, JaCVAM, Health Canada
  - Nearly 200 scientists, 13 countries
- Workshop Output:
  - Procedia in Vaccinology 5: 1-266 (2011)
  - Recommendations for implementation and use of alternative methods
  - Priorities for future work needed to advance alternatives
  - Enhanced International harmonization
  - Vaccine-specific workshops for priority areas:
    - Rabies (2011)
    - Leptospirosis (2012)
    - **Pertussis vaccines-HIST (2012)**
    - Clostridials and diphtheria (2013)

http://www.sciencedirect.com/science/article/pii/S1877282X11000245

International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing

- October 2011: Organized by NICEATM-ICCVAM with ICATM partners
  - National Centers for Animal Health, Ames, Iowa
  - Sponsors: NICEATM, USDA, ECVAM
- 80 participants, 12 countries
- Workshop addressed:
  - Refinement (less pain and distress)
  - Reduction
  - Replacement
- Report published in *Biologicals* 2012
  - Vol 40, No 5, pp 369-381
  - Summary of workshop presentations, discussions, and recommendations

NICEATM-ICCVAM Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing

- September 19-21, 2012
- USDA Centers for Animal Heath Ames, Iowa, USA
- Co-organized with ICATM partners
- Addressed:
  - How to further implement replacement methods for potency testing
  - How to further reduce and refine testing until complete replacement
- Experts from government, academia and industry
- Plenary and Breakout Sessions
- Poster Session
- Workshop proceedings to be published in *Biologicals* in 2013

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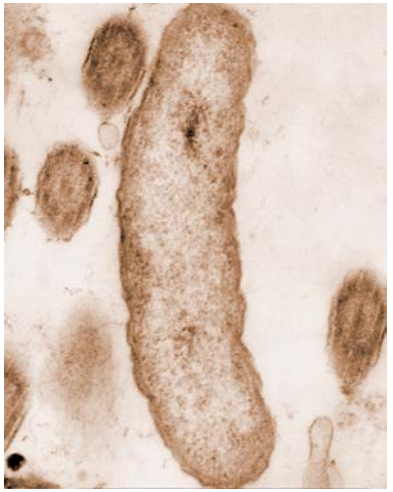
Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines

- November 28-29, 2012
- William H. Natcher Conference Center
  National Institutes of Health,
  Bethesda, MD
- Experts from government, academia and industry expected to attend
- Plenary and Breakout Group Sessions
- NICEATM coordinating with the International working group on alternatives to HIST
- Review of *in vitro* safety data on spiked Pertussis toxin vaccine preparations
- Workshop report to be published
- 47 registrants to date from 11 countries

Further information, including registration, is available at:
http://iccvam.niehs.nih.gov/meetings/HISTWksp-2012/HISTWksp.htm

Pertussis (Whooping Cough)



- Highly contagious disease caused by the bacterium *Bordetella pertussis* and characterized by violent coughing
- Whole cell vaccine introduced in the 1940s
  - Replaced by an acellular vaccine over the last 20 years
- Periodic epidemics every 3 to 5 years and frequent outbreaks
  - During past 5 years, 10,000 to 27,000 cases reported annually in the US
- Murine HIST is a key safety test performed to assay for residual active pertussis toxin prior to vaccine release
  - Based on the sensitization to histamine induced by active pertussis toxin
  - Requires large numbers of laboratory animals (mice) that experience unrelieved pain and distress

Pertussis Vaccine Safety Testing: Priority Activity (1)

- At the September 2010 workshop[1], Pertussis vaccines were identified as one of the three highest priorities for human vaccines for future research, development, and validation efforts because:
  - Many lots are produced annually
  - HIST use large numbers of laboratory animals
  - HIST involves significant unrelieved pain and distress in mice
  - HIST is highly variable often requiring frequent retests

[1]Stokes et al. 2011 The International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: Introduction and Summary. Procedia in Vaccinology 5:1-15.

Pertussis Vaccine Safety Testing: Priority Activity (2)

- Previous HIST workshops[1,2] established an International Working Group on Alternatives to HIST for testing alternative *in vitro* methods using standardized acellular pertussis vaccines and pertussis toxin
  - 12 international laboratories involved
  - 7 vaccines from 3 manufacturers (GlaxoSmithKline, Sanofi Pasteur, Statens Serum Institute)
  - Standardized pertussis toxin spiking protocol
  - Study conducted Summer 2012

[1]Workshop on Animal-Free Detection of PTx in Vaccines – Alternatives to HIST, PEI, Langen, Germany, June 9-10, 2011.
[2]Alternative Safety Testing Strategies for Acellular Pertussis Vaccines (8th World Congress Satellite meeting), Montreal, Canada, August 21, 2011

Acknowledgements:
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