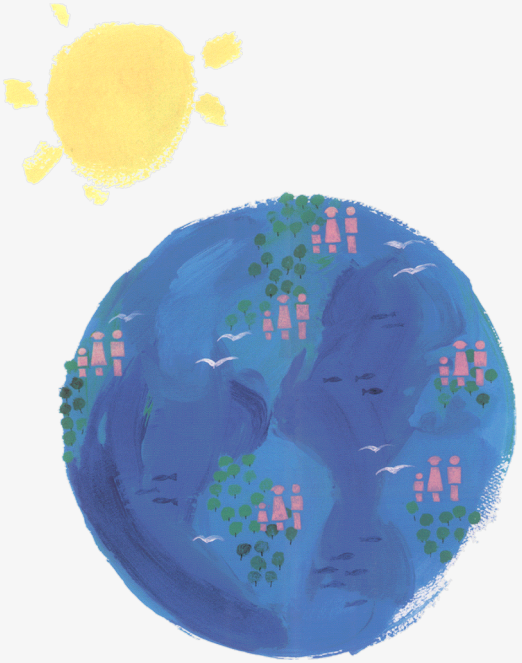
NICEATM

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

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods



Workshop on Acute Chemical Safety Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluation

Welcome and Introduction

William Stokes, D.V.M, D.A.C.L.A.M.
RADM, U.S.Public Health Service
Executive Director, ICCVAM

February 7, 2008
Natcher Conference Center
Bethesda, Maryland

National Toxicology Program

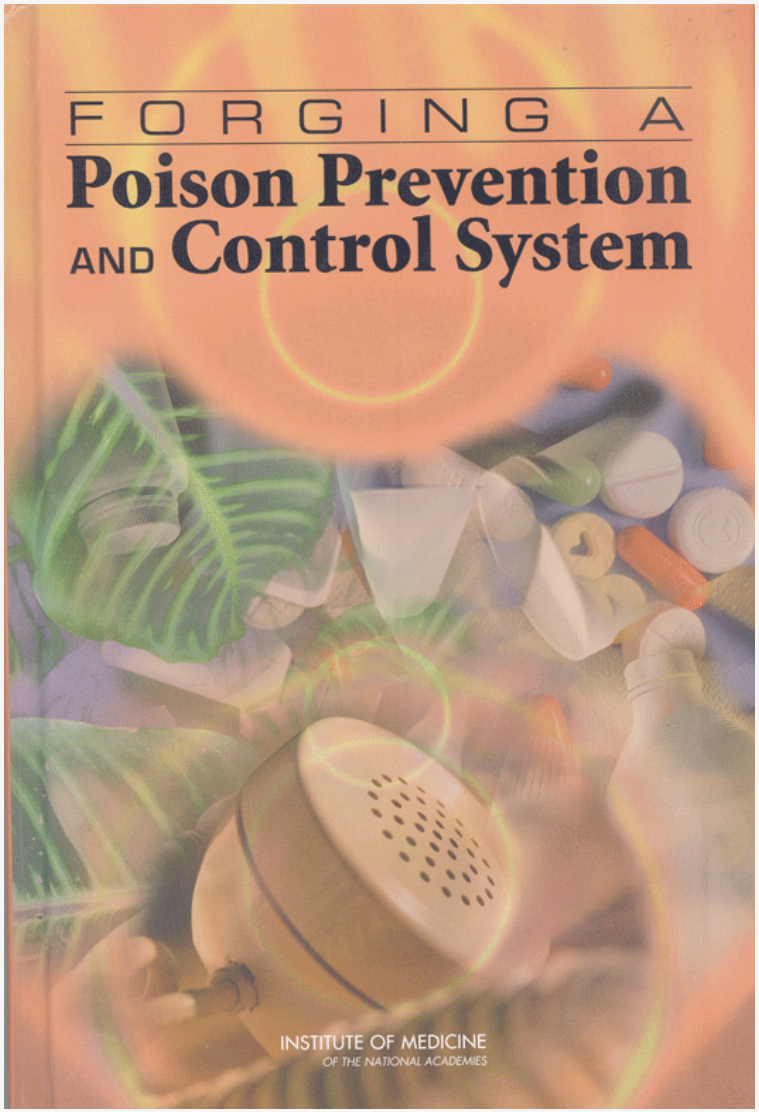
NIEHS

Rationale for This Workshop

- Alternatives for acute systemic toxicity testing is one of ICCVAM's four highest priorities
  - Worldwide, it is the most commonly required product safety test
  - It can result in significant pain and distress to test animals

- Implements activity in the NICEATM - ICCVAM *Five-Year Plan: Convene a workshop to:*
  - *Identify standardized procedures for collecting mechanistic information from in vivo acute oral toxicity testing to aid in developing batteries of predictive in vitro test methods that can further reduce and eventually replace animals*
  - *Seek more predictive humane endpoints that may be used to terminate studies earlier in order to further reduce pain and distress approaches that would further reduce the potential pain and distress*

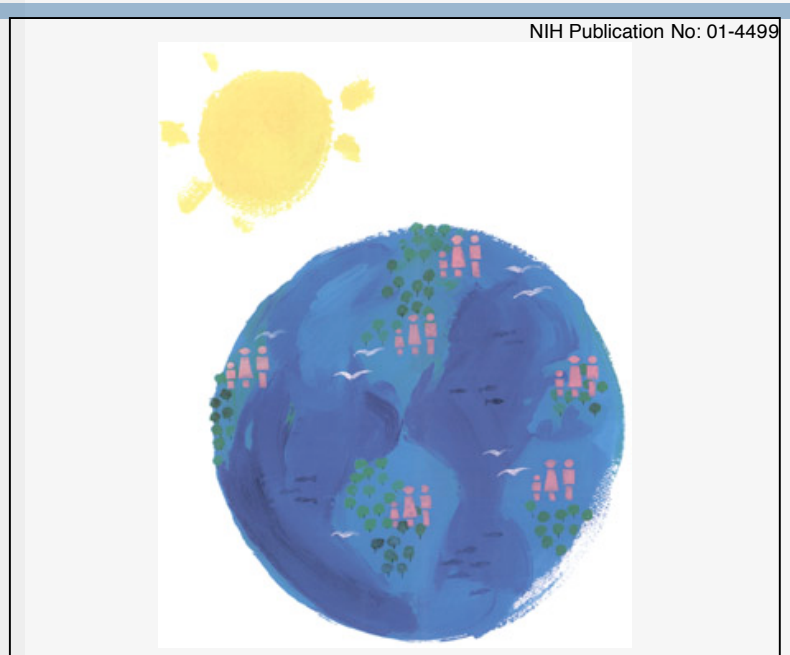
Why is acute toxicity testing important?



- Poisoning is a serious public health issue
- The Institute of Medicine estimates that more than 4 million poisoning episodes occur annually in the United States (IOM 2004).
- In 2001, poisoning was the second leading cause of injury-related deaths (30,800), only exceeded by automobile accidents (42,433 deaths)
- Acute toxicity testing provides basis for accurate hazard labelling and risk management practices

Institute of Medicine. 2004. Forging a Poison Prevention and Control System. Washington: National Academies Press.

International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity

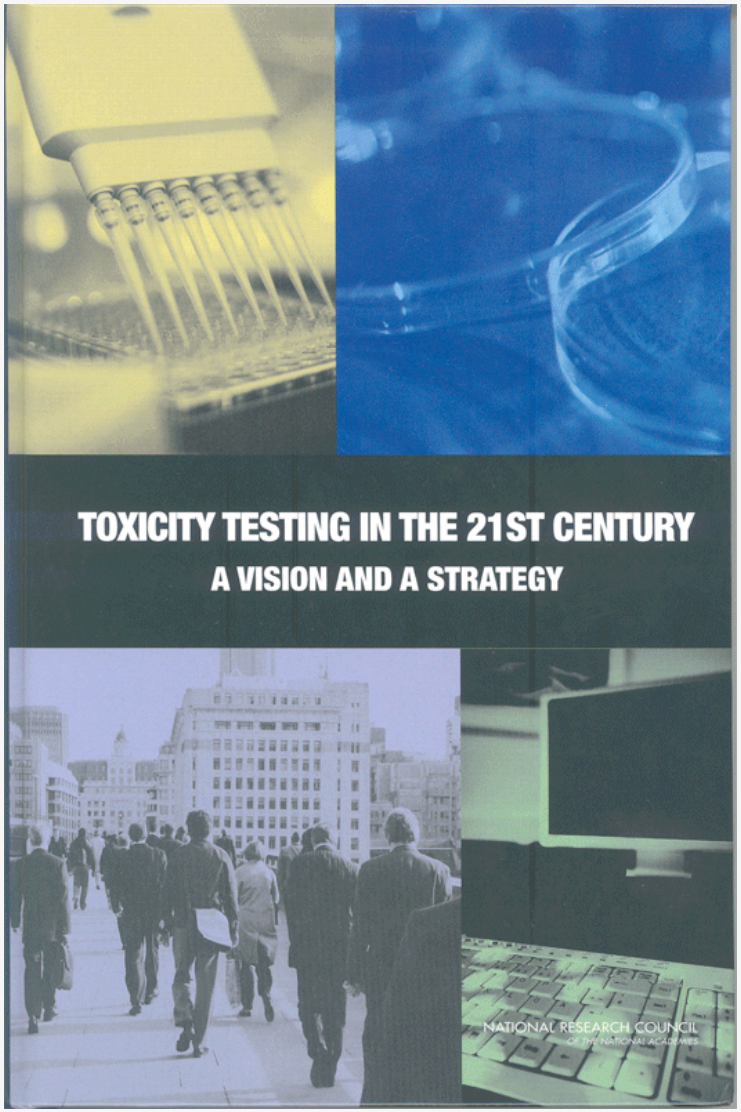


- October 2000
- Workshop recommendations:
  - Short-term goal: Reduce animal use for acute systemic toxicity assays with *in vitro* methods to estimate starting doses
  - Long-term goal: Replace animals with *in vitro* methods that predict human acute systemic toxicity using human cells and tissues

ICCVAM and Alternative Methods for Acute Oral Toxicity Testing

- Revised Up-and-Down Procedure, 2001
  - Reduces animal use by 70%
- *In vitro* methods recommended to further reduce animal use up to 50% per test, 2007
- February 6-7, 2008 Workshop:
  - *Advancing In Vitro Approaches and Humane Endpoints for Systemic Toxicity Evaluations*

Toxicity Testing in the 21st Century



Committee on Toxicity and Assessment of Environmental Agents, National Research Council (2007)

Envisions the significant reduction and replacement of animal use with batteries of predictive *in vitro* assays to evaluate alterations to key toxicity pathways that can be elucidated using a systems biology approach.

NTP's Vision for the 21st Century

- Supports the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations in cell systems and short-term animal studies

http://ntp.niehs.nih.gov/ntpweb/

How can this Workshop contribute to this shared vision?

- Development of predictive pathway-based methods for acute systemic toxicity testing can provide a **proof-of-concept** for application of this vision to regulatory testing

- Workshop will contribute by developing approaches to identify the key toxicity pathways for acute systemic toxicity
  - *In vivo* key pathway information that can be used to identify and develop the necessary *in vitro* methods needed for accurate predictions
  - *In vivo* mechanistic information that may identify predictive biomarkers of systemic toxicity that could be used as earlier, more humane endpoints during *in vivo* tests to further reduce pain and distress
    - **Predictive vs. overt toxicity**

Opening Remarks

Marilyn Wind, Ph.D.
Consumer Product Safety Commission
Chair, ICCVAM

ICCVAM

- Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
- Formed by the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH)
- ICCVAM is a permanent interagency committee of NIEHS under the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
- ICCVAM is composed of representatives from 15 Federal regulatory and research agencies that use, generate or disseminate toxicological information

History of ICCVAM

1994: *ad hoc* ICCVAM established in response to NIEHS directives in the 1993 NIH Reauthorization Act to:

- Develop criteria for validation and regulatory acceptance of test methods.
- Develop a process to achieve regulatory acceptance of scientifically validated methods.

1997: Final report of the *ad hoc* ICCVAM

1997: ICCVAM established

- Replaced *ad hoc* ICCVAM
- Implemented NIEHS directives: P.L. 103-43

1998: NICEATM established

2000: ICCVAM Authorization Act of 2000: P.L. 106-545

- Established “permanent” ICCVAM

ICCVAM's Mission[1]

- To *facilitate* 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

[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

ICCVAM Agency Representatives

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

Consumer Product Safety Commission
• Marilyn L. Wind, Ph.D. (Chair)
* Joanna Matheson, Ph.D.
* Kristina Hatlelid, Ph.D.

Department of Agriculture
• Jodie Kulpa-Eddy, D.V.M. (Vice Chair)
◊ Elizabeth Goldentyer, D.V.M.

Department of Defense
• Robert E. Foster, Ph.D.
◊ Patty Decot
* Peter J. Schultheiss, D.V.M., D.A.C.L.A.M
* Harry Salem, Ph.D.

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

Department of the Interior
• Barnett A. Rattner, Ph.D.
◊ Sarah Gerould, Ph.D.

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

Environmental Protection Agency
Office of Science Coordination and Policy
• Karen Hamernik, Ph.D.
Office of Research and Development
◊ Julian Preston, Ph.D.
* Suzanne McMaster, Ph.D.
OECD Test Guidelines Program
* Jerry Smrchek, Ph.D.
Office of Pesticides Programs
* Amy Rispin, Ph.D.
* Deborah McCall

Food and Drug Administration
Office of Science and Health Coordination
• Suzanne Fitzpatrick, Ph.D., D.A.B.T.
Center for Drug Evaluation and Research
◊ Abigail C. Jacobs, Ph.D.
Center for Devices and Radiological Health
* Melvin E. Stratmeyer, Ph.D.
Center for Biologics Evaluation and Research
* Richard McFarland, Ph.D., M.D.
* Ying Huang, Ph.D.
Center for Food Safety and Nutrition
* David G. Hattan, Ph.D.
* Robert L. Bronaugh, Ph.D.
Center for Veterinary Medicine
* Devaraya Jagannath, Ph.D.
* M. Cecilia Aguila, D.V.M.
National Center for Toxicological Research
* William T. Allaben, Ph.D.
* Paul Howard, Ph.D.
Office of Regulatory Affairs
* Lawrence A. D'Hoostelaere, Ph.D.

National Cancer Institute
• Alan Poland, M.D.
◊ T. Kevin Howcroft, Ph.D.

National Institute of Environmental Health Sciences
• William S. Stokes, D.V.M., D.A.C.L.A.M.
◊ Raymond Tice, Ph.D.
* Rajendra S. Chhabra, Ph.D., D.A.B.T
* Jerrold J. Heindel, Ph.D.

National Institute for Occupational Safety and Health
• Paul Nicolaysen, V.M.D.
◊ K. Murali Rao, MD, Ph.D.

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

National Library of Medicine
• Jeanne Goshorn, M.S.

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

• Principal Agency Representative
◊ Alternate Principal Agency Representative
* Other Designated Agency Representatives

Acute Toxicity Working Group (ATWG)

- **Consumer Product Safety Commission (CPSC)**
  - Marilyn Wind, Ph.D. (ICCVAM Chair, ATWG Chair)
  - Cassandra Prioleau, Ph.D.
- **Environmental Protection Agency (EPA)**
  - Karen Hamernik, Ph.D.
  - Masih Hashim, Ph.D.
  - Marianne Lewis
  - Debbie McCall
  - Elizabeth Margosches, Ph.D.
  - John Redden, Ph.D.
  - Amy Rispin, Ph.D.
- **Food and Drug Administration (FDA)**
  - Abigail Jacobs, Ph.D.
  - Suzanne Morris, Ph.D.
  - Thomas Umbreit, Ph.D.
- **National Institute of Environmental Health Sciences (NIEHS)**
  - Rajendra Chhabra, Ph.D., DABT
  - William Stokes, D.V.M., DACLAM
  - Raymond Tice, Ph.D.
- **National Institute for Occupational Safety and Health (NIOSH)**
  - Steven Reynolds, Ph.D.
- **ECVAM Liaison**
  - Pilar Prieto, Ph.D.
- **JaCVAM Liaison**
  - Hajime Kojima, Ph.D.

NICEATM

- The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM or "the Center") was established in 1998 to:
  - Administer ICCVAM and its scientific advisory committee
  - Provide technical/scientific support and coordination for ICCVAM and ICCVAM working groups
  - Assist with ICCVAM activities, such as peer reviews and workshops
  - Conduct independent validation studies
  - Provide mechanism for communication between agencies test method developers, and stakeholders

NICEATM Staff

- **NIEHS**
  - William S. Stokes, D.V.M., DACLAM — Director; Project Officer
  - Raymond Tice, Ph.D. — Deputy Director
  - Debbie McCarley — Special Assistant; Asst. Project Officer

- **Center Support Contract (ILS, Inc.)**
  - David Allen, Ph.D. — Principal Investigator
  - Douglas Winters, M.S. — Project Manager
  - Thomas Burns, M.S. — Sr. Project Coordinator/Technical Writer
  - Patricia Ceger, M.S. — Project Coordinator/Technical Writer
  - Frank Deal, M.S. — Staff Toxicologist
  - Elizabeth Lipscomb, Ph.D. — Staff Toxicologist
  - Linda Litchfield — Administrative Asst./Meeting Planner
  - Michael Paris — Sr. Project Coordinator/Technical Writer
  - Eleni Salicru, Ph.D. — Staff Toxicologist
  - Catherine Sprankle — Web Developer/Communication Specialist
  - Judy Strickland, Ph.D., DABT — Sr. Staff Toxicologist
  - Jim Truax, M.S. — Project Coordinator/Technical Writer

Workshop Overview

Workshop Goals

- Review the state-of-the-science and identify knowledge gaps (at the whole organism, organ system, cellular, and/or molecular levels) regarding the key *in vivo* pathways involved in acute systemic toxicity
- Recommend how these knowledge gaps can be addressed by collecting mechanistic biomarker data during currently required *in vivo* safety testing
- Recommend how *in vivo* key pathway information can be used to develop more predictive mechanism-based *in vitro* test systems and to identify biomarkers that may serve as predictive earlier more humane endpoints for *in vivo* test methods
- Recommend how mechanism-based *in vitro* test systems and earlier more humane endpoints can be used to further reduce, refine, and eventually replace animal use for acute systemic toxicity testing while ensuring the protection of human and animal health.

Workshop Objectives (1)

1. Discuss the current understanding of key pathways for *in vivo* acute systemic toxicity and identify the knowledge gaps that exist, especially for
   (1) *in vivo* pathways, and
   (2) chemicals and products tested for acute systemic toxicity
2. Identify and prioritize future research initiatives that would address these knowledge gaps and that are considered necessary to advance the development and validation of *in vitro* methods for assessing acute systemic toxicity.
3. Review molecular, cellular, tissue, or other physiological, and clinical biomarkers that are or could be measured or observed during *in vivo* acute systemic toxicity testing and discuss their potential usefulness for indicating key pathways of acute systemic toxicity.
4. Discuss how the key toxicity pathways indicated by these *in vivo* measurements and observations might be modeled using alternative *in vitro* test methods.

Workshop Objectives (2)

5. Discuss and identify observations and quantitative, objective measurements that could or should be included in the current *in vivo* acute systemic toxicity tests to elucidate key toxicity pathways that would support the future development and validation of predictive *in vitro* methods.
6. Identify and prioritize research, development, and validation activities for *in vitro* test methods that model the key *in vivo* toxicity pathways and more accurately predict acute systemic toxicity hazard categories.
7. Discuss what *in vivo* data collected to elucidate key toxicity pathways might lead to the identification and validation of more humane endpoints for acute systemic toxicity testing, and what data should be a priority for collection to aid in identifying earlier more humane endpoints.
8. Discuss how to promote the collection and submission of *in vitro* and *in vivo* toxicity test data to ICCVAM in order to advance the development and validation of more predictive *in vitro* test methods and earlier more humane endpoints for acute systemic toxicity testing.

Workshop Agenda (1)

Day 1	**Wednesday, February 6, 2008**
8:00 a.m.	Registration
9:00 a.m.	Session 1 - Acute Systemic Toxicity: Public Health Significance and Regulatory Testing Needs
9:50 a.m.	Session 2 - Acute Systemic Toxicity: Human and Animal Assessments, Biomarkers, and Key Pathways
10:10 a.m.	Break
10:30 a.m.	Continue Session 2
11:50 a.m.	Lunch

Workshop Agenda (2)

Day 1	**Wednesday, February 6, 2008 (continued)**
12:50 p.m.	Continue Session 2
1:35 p.m.	Break
1:50 p.m.	Concurrent Breakout Group Discussions **Breakout Group 1: Key Pathways for Acute Systemic Toxicity** **Breakout Group 2: Current Acute Systemic Toxicity Injury and Toxicity Assessments**
3:20 p.m.	Break
3:35 p.m.	Concurrent Breakout Group Discussions (continued)
5:00 p.m.	Breakout Groups Adjourn

Workshop Agenda (3)

Day 2 Thursday, February 7, 2008

8:30 a.m.	Plenary Session - Discussion and Recommendations Reached by Breakout Groups 1 and 2
9:10 a.m.	Session 3 - Humane Endpoints
10:00 a.m.	Break
10:15 a.m.	Session 4 - State of the Science: Using *In Vitro* Methods to Predict Acute Systemic Toxicity
12:05 p.m.	Lunch

Workshop Agenda (4)

Day 2	**Thursday, February 7, 2008 (continued)**
1:00 p.m.	Concurrent Breakout Group Discussions **Breakout Group 3: Identifying Earlier Humane Endpoints for Acute Systemic Toxicity Testing** **Breakout Group 4: Application of *In Vivo* Mode of Action and Mechanistic Information to the Development and Validation of *In Vitro* Methods for Assessing Acute Systemic Toxicity** **Breakout Group 5: Industry Involvement in Test Method Development, Validation, and Use**
2:20 p.m.	Break
2:35 p.m.	Concurrent Breakout Group Discussions (continued)
3:35 p.m.	Break
3:50 p.m.	Plenary Session - Discussion and Recommendations Reached by Breakout Groups 3, 4, and 5
4:50 p.m.	Closing Comments - End of Meeting