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 Evaluations

I. Introduction and Objectives

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National Toxicology Program

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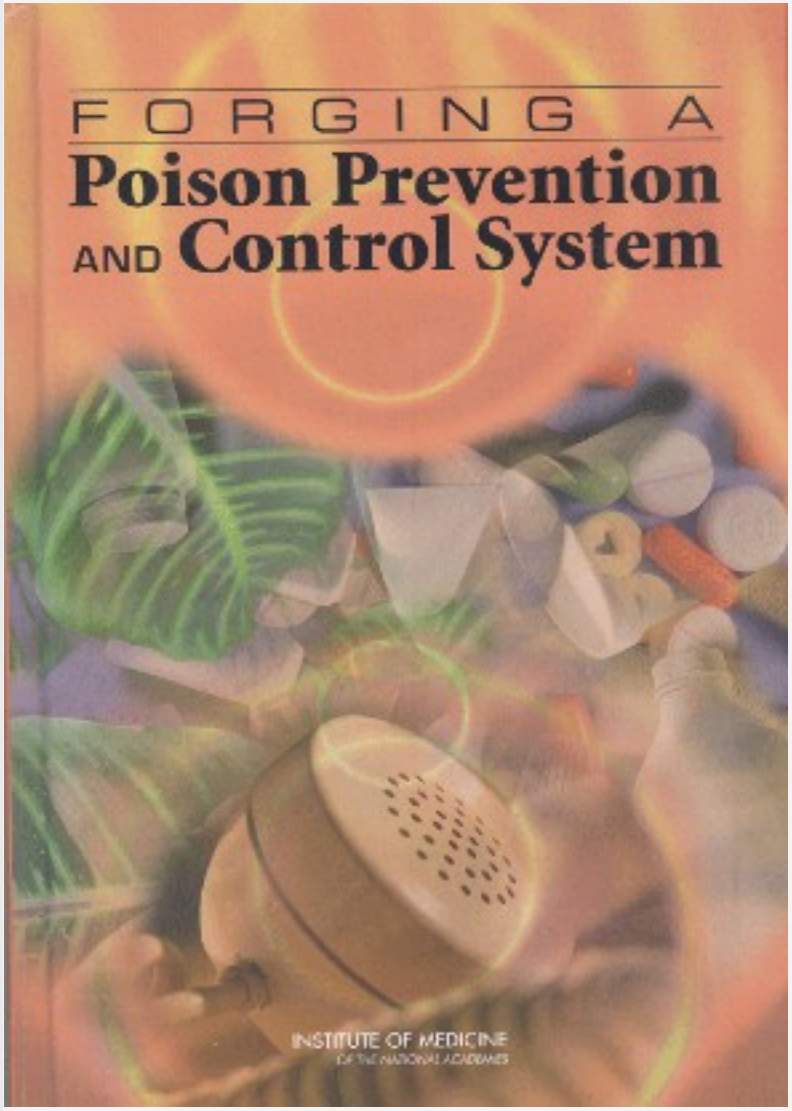
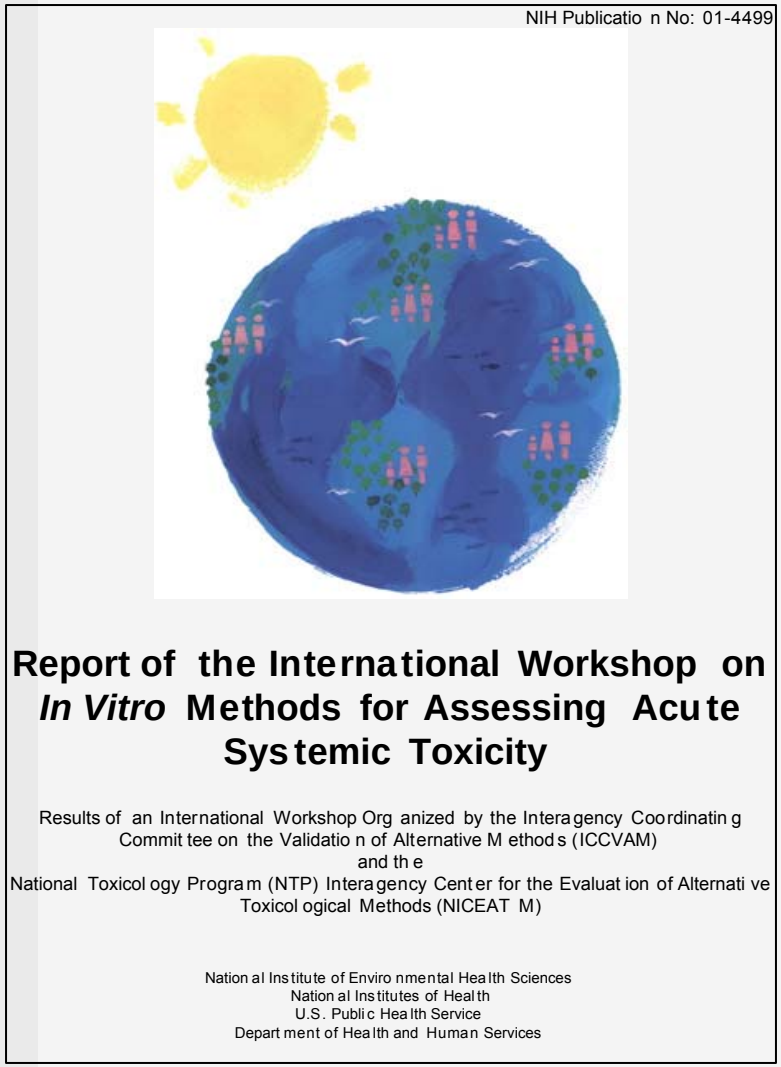
Why is Safety Testing for Acute Toxicity Important?



- **Poisoning is a serious public health issue**
- Institute of Medicine estimates more than 4 million poisonings occur annually in the United States (IOM 2004).
- Poisoning: the second leading cause of injury-related deaths (30,800) in 2001
  - only exceeded by automobile accidents (42,433 deaths)
- Safety testing provides basis for:
  - Accurate hazard labeling
  - Risk management practices
  - Informed treatment decisions

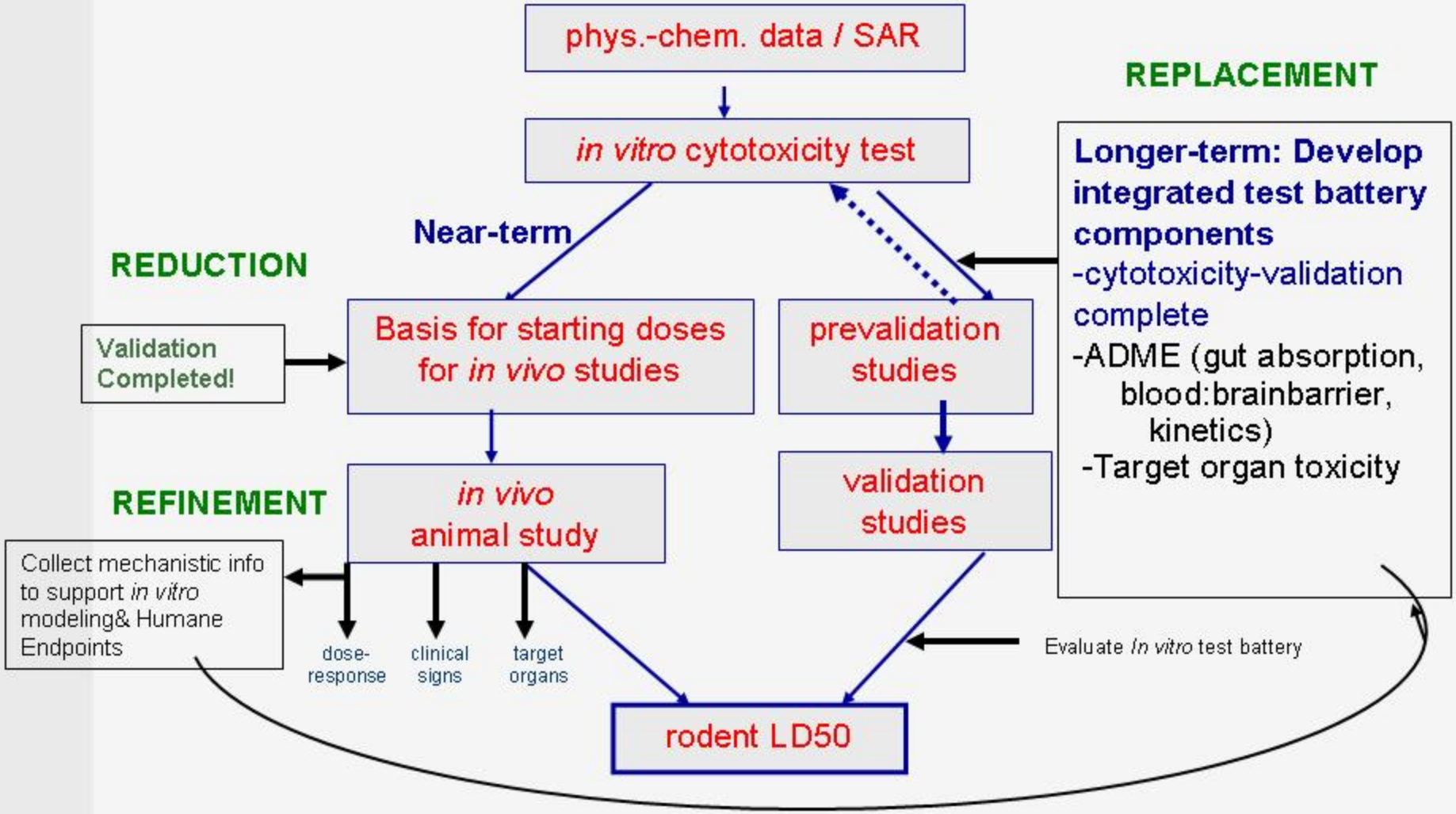
Institute of Medicine. 2004. Forging a Poison Prevention and Control System. Washington: National Academies Press.

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



- October 2000
- Reviewed the validation status of in vitro approaches for acute systemic toxicity
- Workshop recommendations:
  - Short-term goal:
    Reduce animal use for acute systemic toxicity assays with *in vitro* methods to estimate starting doses for animal studies
  - Long-term goal:
    Replace animals with an integrated battery of *in vitro* methods that predict human acute systemic toxicity using human cells and tissues

Strategy for the Reduction, Refinement and Replacement of Animals in Acute LD_{50} Testing[1]



[1]Adapted/updated from ICCVAM. 2001. Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity. NIH Publication No. 01-4499. Research Triangle Park, NC:National Institute for Environmental Health Sciences. Available: http://iccvam.niehs.nih.gov/

Ongoing R&D:In Vitro Models for ADME and Target Organ Toxicity

A-Cute-Tox Project

- Implements R&D recommendations from the 2000 ICCVAM workshop
- Overall Aim: Develop a simple and robust *in vitro* testing strategy to predict human acute systemic toxicity, which could replace the animal toxicity tests for regulatory purposes
- An EU Research and Development Integrated Project: partnership of the EDIT* Consortium, ECVAM, and 35 toxicity research group partners:
- Started January 2005; completion January 2010.

*EDIT: Evaluation-guided development of *in vitro* test batteries

*REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

http://www.acutetox.org/

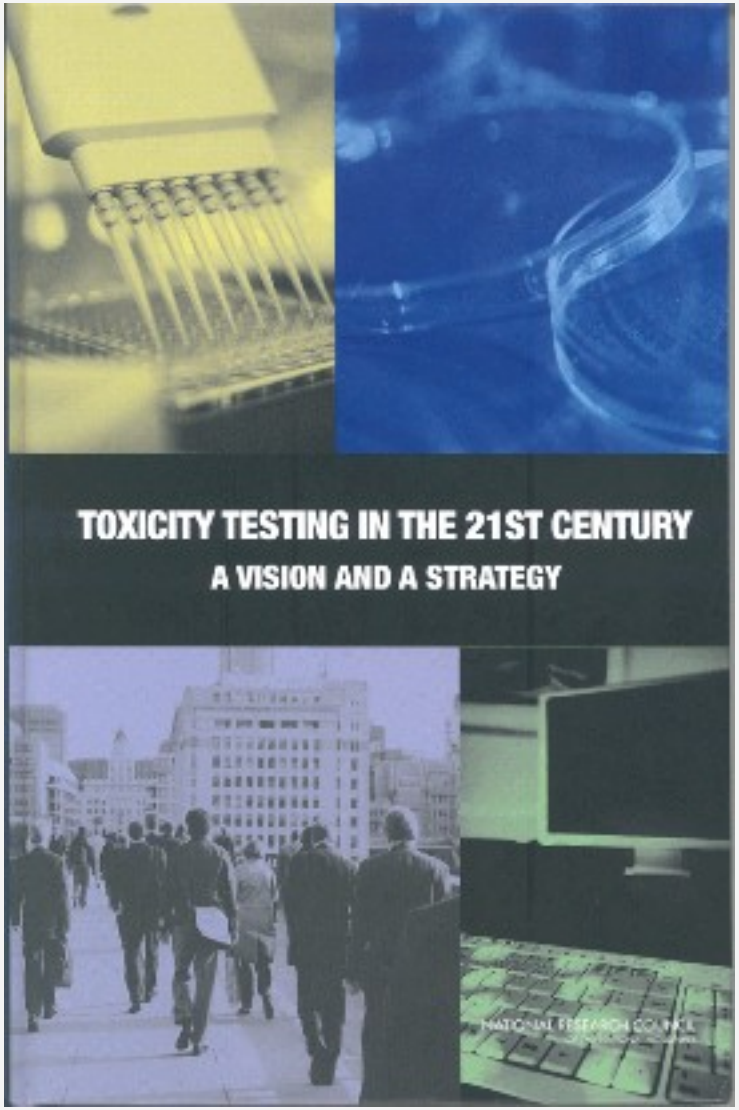
ICCVAM and Alternative Methods for Acute Oral Toxicity Testing

- Revised Up-and-Down Procedure, 2001
  - International regulatory acceptance, 2002
  - Reduces animal use by 70%
- *In vitro* methods recommended to further reduce animal use up to 50% per test, 2008
- February 6-7, 2008 Workshop:
  - *Acute Chemical Safety Testing: Advancing In Vitro Approaches and Humane Endpoints for Systemic Toxicity Evaluations*

Rationale for the 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 and more humane endpoints that may be used to terminate studies earlier in order to further reduce pain and distress*
- ECVAM seeking non-animal approach to meet the March 2009 EU ban on use of animals for acute systemic safety testing of cosmetics

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/

Workshop on Acute Chemical Toxicity Testing

How could this contribute to implementation of the NRC and NTP vision?

- Development of predictive pathway-based methods for acute systemic toxicity testing could provide a **proof-of-concept** for application of this vision to:
  - regulatory testing
  - More complex systemic toxicity assessments
- Workshop to discuss 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 *in vitro* methods needed for accurate predictions
  - *In vivo* mechanistic information that may identify predictive biomarkers that could be used as earlier, more humane endpoints during *in vivo* tests to further reduce or avoid pain and distress, while it is still necessary to use animals

Workshop Overview

- Addressed the collection and use of mechanistic *in vivo* data to target development of:
  - Predictive *in vitro* methods
  - Earlier more humane endpoints
- February 6-7, 2008; NIH, Bethesda, MD
- Organized/sponsored by NICEATM, ICCVAM, ECVAM, and JaCVAM
- 120+ attendees/6 countries represented
- 14 presentations
- 5 breakout groups

Workshop Goals-1

- Review the state-of-the-science and identify knowledge gaps regarding key *in vivo* pathways involved in acute systemic toxicity
  - at the whole organism, organ system, cellular, and/or molecular levels

- Recommend how these knowledge gaps can be addressed by collecting mechanistic biomarker data during currently required *in vivo* safety testing

Workshop Goals-2

- Recommend how *in vivo* key pathway information can be used to:
  - Develop more predictive mechanism-based *in vitro* test systems
  - 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 continued protection of human and animal health

Workshop Sessions

- Session 1:

  Acute Systemic Toxicity: Public Health Significance and Regulatory Testing Needs

- Session 2:

  Acute Systemic Toxicity: Human and Animal Assessments, Biomarkers, and Key Pathways

- Session 3:

  Humane Endpoints

- Session 4:

  State of the Science: Using *In Vitro* Methods to Predict Acute Systemic Toxicity

Workshop Product

- Workshop report on the NICEATM-ICCVAM website
  - Summer 2008

- Workshop Summary in EHP
  - 2008

Acknowledgements: Invited Workshop Participants

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1. How might industry be encouraged to collect mechanistic data in current acute toxicity tests that might lead to the development of earlier more humane endpoints, and the development of more predictive *in vitro* alternative test method strategies?
2. The participants outlined a number of recommendations for incorporating humane endpoints into current acute toxicity evaluations. Please comment on how these recommendations can best and most efficiently be implemented by industry.
3. How might the data gaps and research needs identified in the report that will be necessary to further advance earlier humane endpoints and in vitro approaches best be addressed by the scientific community?