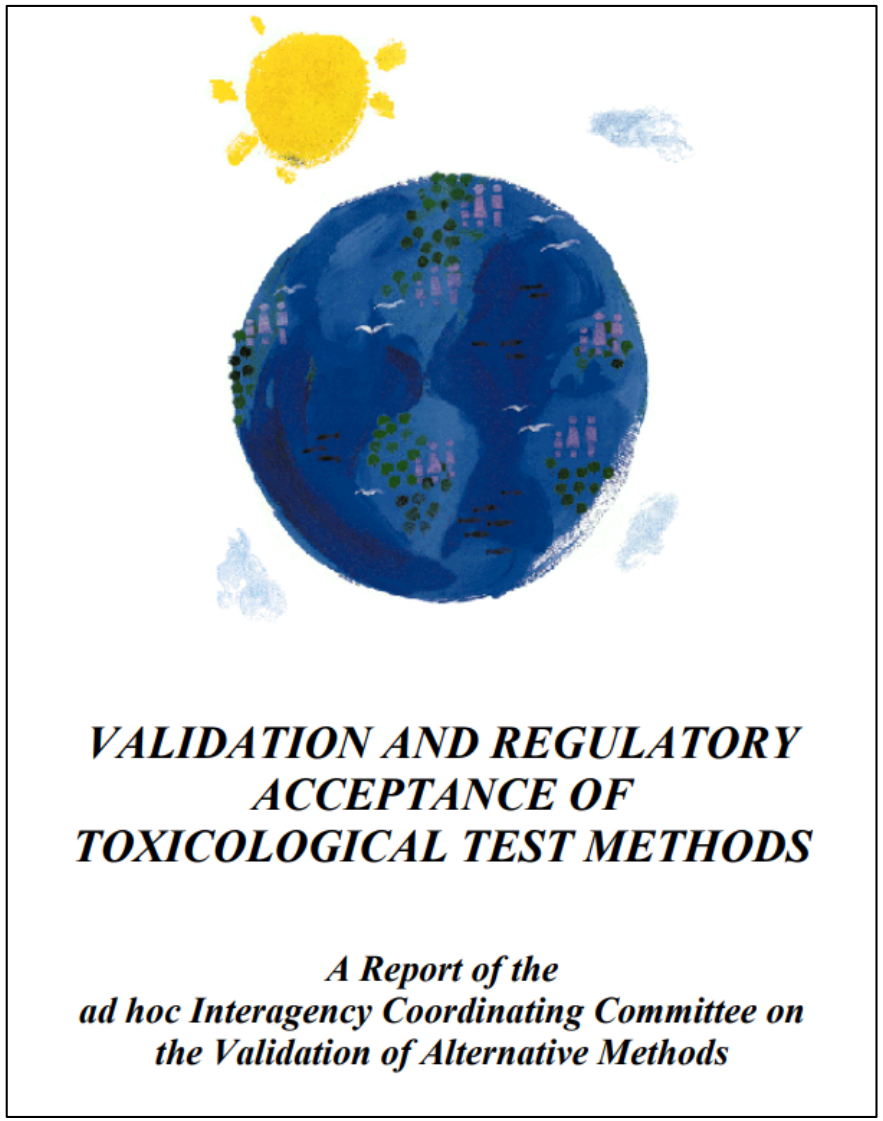
Reflections on 20 Years of ICCVAM

Linda Birnbaum, Ph.D., DABT

May 21, 2020

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

In the beginning, there was an ad hoc committee…



ICCVAM Authorization Act of 2000

PUBLIC LAW 106–545 (42 U.S.C. 285*l*-3):

"To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness."

- Consumer Product Safety Commission
- Department of Agriculture
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- Occupational Safety and Health Administration
- National Institute for Occupational Safety and Health
- Agency for Toxic Substances and Disease Registry
- National Cancer Institute
- National Inst of Env. Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy
- National Institute of Science and Technology (since 2017)

Public Law 106–545
106th Congress

An Act

To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness.

Dec. 19, 2000
[H.R. 4281]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

ICCVAM Authorization Act of 2000. 42 USC 201 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "ICCVAM Authorization Act of 2000".

42 USC 285*l*-2.

SEC. 2. DEFINITIONS.

In this Act:

(1) ALTERNATIVE TEST METHOD.—The term "alternative test method" means a test method that—

(A) includes any new or revised test method; and

(B)(i) reduces the number of animals required;

(ii) refines procedures to lessen or eliminate pain or distress to animals, or enhances animal well-being; or

(iii) replaces animals with non-animal systems or one animal species with a phylogenetically lower animal species, such as replacing a mammal with an invertebrate.

(2) ICCVAM TEST RECOMMENDATION.—The term "ICCVAM test recommendation" means a summary report prepared by the ICCVAM characterizing the results of a scientific expert peer review of a test method.

42 USC 285*l*-3.

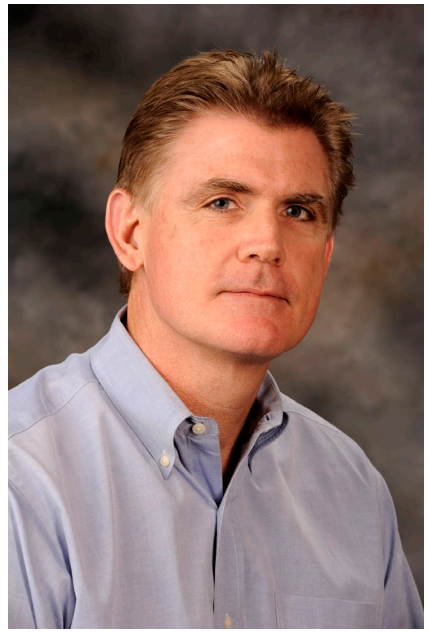
SEC. 3. INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS.

(a) IN GENERAL.—With respect to the interagency coordinating committee that is known as the Interagency Coordinating Committee on the Validation of Alternative Methods (referred to in this Act as "ICCVAM") and that was established by the Director of the National Institute of Environmental Health Sciences for purposes of section 463A(b) of the Public Health Service Act, the Director of the Institute shall designate such committee as a permanent interagency coordinating committee of the Institute under the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods. This Act may not be construed as affecting the authorities of such Director regarding ICCVAM that were in effect on the day before the date of the enactment of this Act, except to the extent inconsistent with this Act.

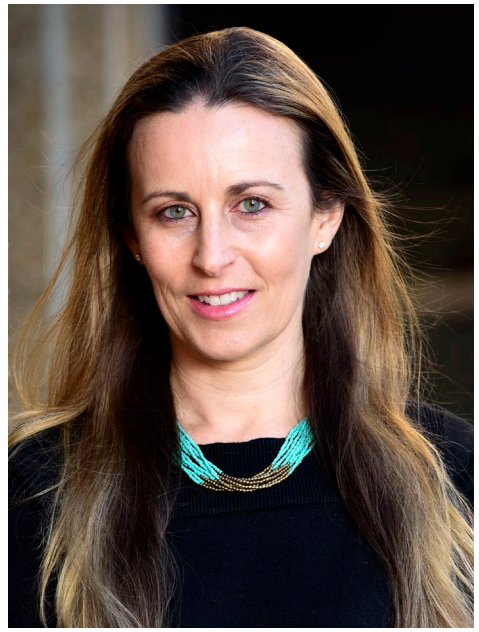
NICEATM Leadership

Bill Stokes
Director
(1997-2012)

Ray Tice
Deputy Director
(2005-2010)



Warren Casey
Director (2013-2020)
Deputy Director (2010-2013)



Nicole Kleinstreuer
Acting Director (2020-present)
Deputy Director (2017-2020)

ICCVAM Chairs, Vice-chairs, and Co-chairs

- Richard Hill, EPA
- Leonard Schechtman, FDA
- Marilyn Wind, CPSC
- Jodie Kulpa-Eddy, USDA
- Joanna Matheson, CPSC
- Anna Lowit, EPA
- Abigail Jacobs, FDA
- Emily Reinke, DoD






ICCVAM Advisory Committee



- Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)
- Meets annually in public session to advise ICCVAM, NICEATM, and the NIEHS Director on ICCVAM activities
- Created by the ICCVAM Authorization Act
- Includes members from regulated industries, animal welfare organizations, academia, test method developers, and other ICCVAM stakeholder groups

ICCVAM Stakeholders

- U.S. Federal agencies that generate, require, or use toxicological data
- Agencies within governments of other countries that use or generate toxicological data
- Researchers and Institutional Animal Care and Use Committee (IACUC) members in companies or research institutions that perform toxicological testing
- Companies that develop toxicological tests
- Animal welfare organizations
- Consumer protection organizations
- The public

ICCVAM Workgroups and Subcommittees

- Acute Toxicity
- Biologics
- Biomarkers
- Botulinum Toxin
- Dermal Irritation
- Ecotoxicology
- Endocrine Disruptors
- Genetic Toxicity
- Immunotoxicity
- In Vitro to In Vivo Extrapolation
- Metrics
- Nanomaterials
- Ocular Irritation
- Pyrogen
- Read Across
- Research and Development
- Skin Sensitization
- Strategic Roadmap

20 YEARS OF ICCVAM
Advancing Alternatives to Animal Testing

An ICCVAM Timeline

1997: Ad hoc committee recommends establishment of permanent ICCVAM Committee

2000: ICCVAM Authorization Act passed establishing 15-agency committee

1999 – 2012: ICCVAM recommendations on alternatives for eye/skin irritation, skin sensitization, acute toxicity, endocrine disruptors, pyrogen testing

2009: International Cooperation on Alternative Test Methods (ICATM) established by ICCVAM and partners in the EU, Japan, and Canada

2011: ICATM expanded to include South Korea

2013: Reinvention of ICCVAM; new focus on agency leadership, specific goals, and stakeholder engagement

2013 – 2020: Increased focus on computational toxicology, Tox21 support, and AOPs. ICCVAM-recommended alternatives implemented in regulatory policy for acute toxicity, endocrine disruption, and skin sensitization

2014: First ICCVAM Public Forum

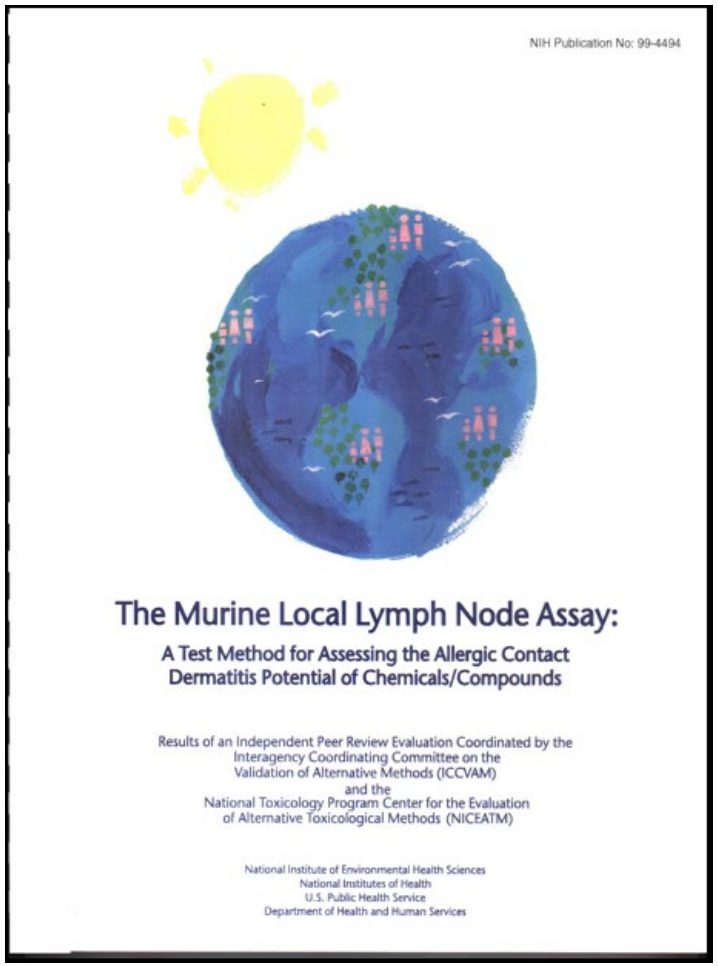
2015: First ICCVAM ICCVAM Communities of Practice webinar

2017: NIST joins ICCVAM

2018: U.S. Strategic Roadmap published

1997 1998 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020

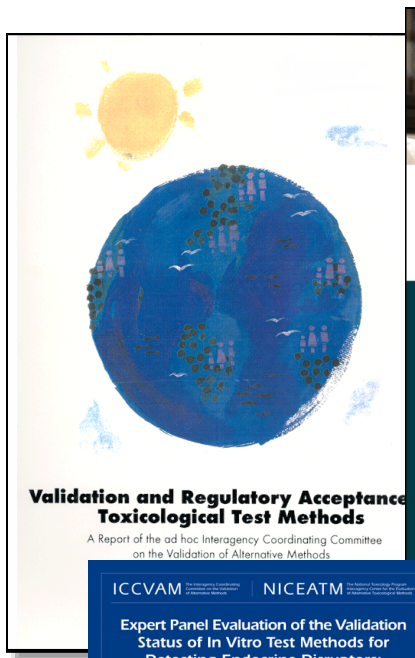
The Local Lymph Node Assay: An ICCVAM First

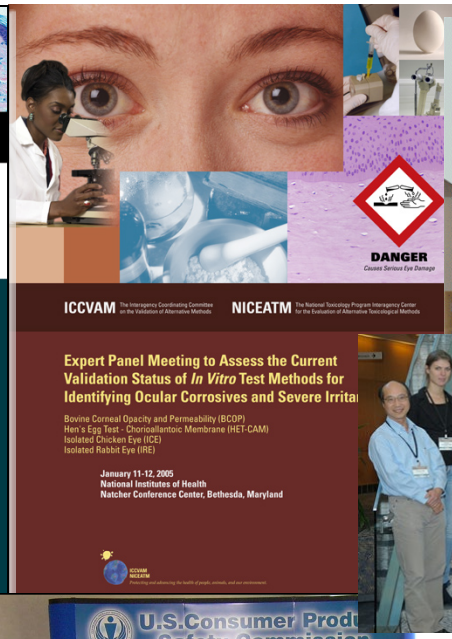


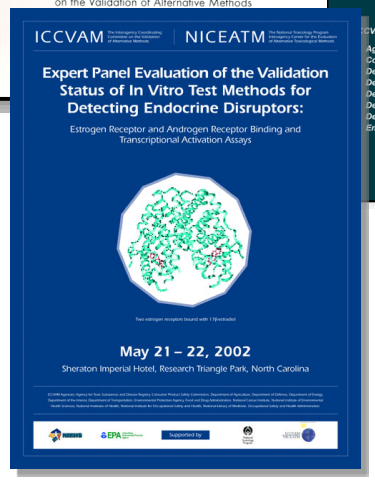
https://ntp.niehs.nih.gov/go/40482

- First method submitted to ICCVAM, 1997
- Sponsors:
  - Dr. F. Gerberick, P&G
  - Dr. D. Basketter, Unilever
  - Dr. I. Kimber, Zeneca
- ICCVAM International Peer Review Panel Meeting
  - September, 1998
  - Valid substitute for guinea pig tests
- Regulatory Acceptance
- U.S. EPA, FDA, CPSC
  - October, 1999
- OECD TG 429: 2002

The first 10 years – Validation and Peer Review







International Partners - ICATM

- International Cooperation on Alternative Toxicological Methods

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Environmental Health Sciences (NIEHS)

For Immediate Release
Monday, April 27, 2009

Contact:
Robin Mackar, NIEHS
(919) 541-0073

Countries Unite to Reduce Animal Use in Product Toxicity Testing Worldwide
U.S., Canada, Japan and European Union Sign International Agreement

Representatives from four international agencies, including the director of the U.S. National Toxicology Program (NTP), today signed a memorandum of cooperation that could reduce the number of animals required for consumer product safety testing worldwide. The agreement between the United States, Canada, Japan and the European Union will yield globally coordinated scientific recommendations on alternative toxicity testing methods that should speed their adoption in each of these countries, thus reducing the number of animals needed for product safety testing. The memorandum is available at http://iccvam.niehs.nih.gov/docs/about_docs/ICATM-MOC.pdf .

"Signing this international agreement demonstrates our commitment to finding and advancing alternatives to animal testing," said Linda Birnbaum, Ph.D., director of the NTP and National Institute of Environmental Health Sciences, part of the National Institutes of Health. "This agreement will help us achieve greater efficiency by avoiding duplication of effort and allowing us to leverage limited resources."

Birnbaum signed as the U.S. representative on behalf of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), one of the national validation organizations participating in the agreement. Others who signed include Elke Anklam, Ph.D., for the European Centre for the Validation of Alternative Methods (ECVAM), David Blakey, D.Phil., for the Environmental Health Science and Research Bureau within Health Canada, and Masahiro Nishijima, Ph.D. for the Japanese Centre for the Validation of Alternative Methods (JaCVAM).

ICCVAM and NICEATM Recognition: SOT Enhancement of Animal Welfare Award

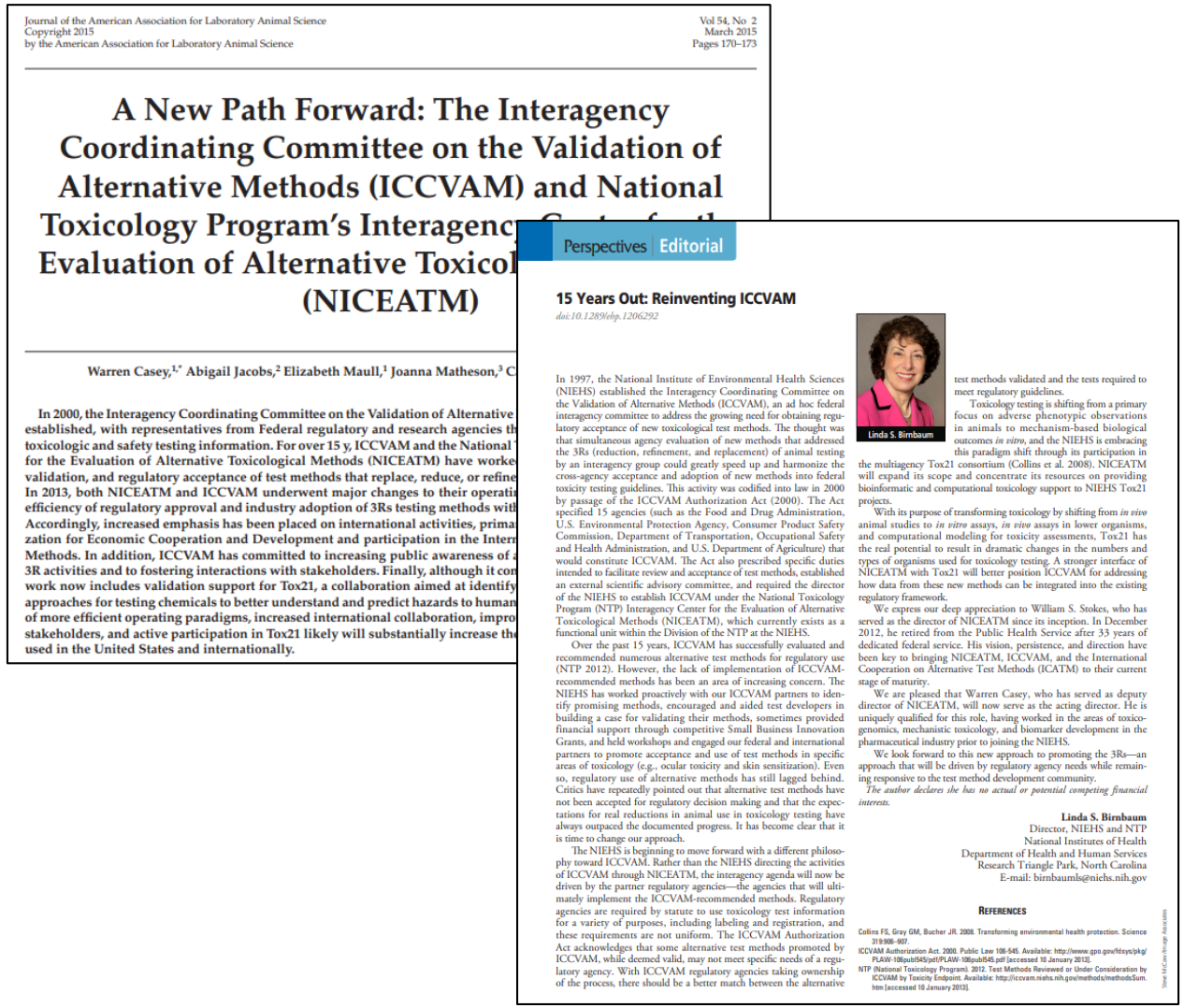
- 2006: William Stokes (NICEATM Director)
- 2010: Leonard Schechtman (former ICCVAM Chair)
- 2016: Warren Casey (NICEATM Director)
- 2017: David Allen (Principal Investigator, ILS NICEATM support contract)
- 2018: Anna Lowit (ICCVAM Co-chair)
- 2019: Suzy Fitzpatrick (ICCVAM member)
- 2020: Kristé Sullivan (PCRM)

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

New Vision and Direction for ICCVAM

- The ICCVAM document: *"A New Vision and Direction for ICCVAM"* describes the *initial steps* towards a new strategic direction for ICCVAM and NICEATM
- Covers three areas:
  - ICCVAM priority setting and science focus areas for immediate ICCVAM resource investment
  - Plans to improve communications with stakeholders and the public
  - Exploring new paradigms for the validation and utilization of alternative toxicological methods



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March 2015
Pages 170–173

A New Path Forward: The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program's Interagenc… Evaluation of Alternative Toxicol… (NICEATM)

Warren Casey,[1,*] Abigail Jacobs,[2] Elizabeth Maull,[1] Joanna Matheson,[3] C…

In 2000, the Interagency Coordinating Committee on the Validation of Alternative… established, with representatives from Federal regulatory and research agencies th… toxicologic and safety testing information. For over 15 y, ICCVAM and the National … for the Evaluation of Alternative Toxicological Methods (NICEATM) have worke… validation, and regulatory acceptance of test methods that replace, reduce, or refine… In 2013, both NICEATM and ICCVAM underwent major changes to their operati… efficiency of regulatory approval and industry adoption of 3Rs testing methods with… Accordingly, increased emphasis has been placed on international activities, prima… zation for Economic Cooperation and Development and participation in the Intern… Methods. In addition, ICCVAM has committed to increasing public awareness of … 3R activities and to fostering interactions with stakeholders. Finally, although it con… work now includes validation support for Tox21, a collaboration aimed at identify… approaches for testing chemicals to better understand and predict hazards to human… of more efficient operating paradigms, increased international collaboration, impro… stakeholders, and active participation in Tox21 likely will substantially increase the… used in the United States and internationally.

Perspectives | Editorial

15 Years Out: Reinventing ICCVAM

doi:10.1289/ehp.1206292

Linda S. Birnbaum

In 1997, the National Institute of Environmental Health Sciences (NIEHS) established the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), an ad hoc federal interagency committee to address the growing need for obtaining regulatory acceptance of new toxicological test methods. The thought was that simultaneous agency evaluation of new methods that addressed the 3Rs (reduction, refinement, and replacement) of animal testing by an interagency group could greatly speed up and harmonize the cross-agency acceptance and adoption of new methods into federal toxicity testing guidelines. This activity was codified into law in 2000 by passage of the ICCVAM Authorization Act (2000). The Act specified 15 agencies (such as the Food and Drug Administration, U.S. Environmental Protection Agency, Consumer Product Safety Commission, Department of Transportation, Occupational Safety and Health Administration, and U.S. Department of Agriculture) that would constitute ICCVAM. The Act also prescribed specific duties intended to facilitate review and acceptance of test methods, established an external scientific advisory committee, and required the director of the NIEHS to establish ICCVAM under the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), which currently exists as a functional unit within the Division of the NTP at the NIEHS.

Over the past 15 years, ICCVAM has successfully evaluated and recommended numerous alternative test methods for regulatory use (NTP 2012). However, the lack of implementation of ICCVAM-recommended methods has been an area of increasing concern. The NIEHS has worked proactively with our ICCVAM partners to identify promising methods, encouraged and aided test developers in building a case for validating their methods, sometimes provided financial support through competitive Small Business Innovation Grants, and held workshops and engaged our federal and international partners to promote acceptance and use of test methods in specific areas of toxicology (e.g., ocular toxicity and skin sensitization). Even so, regulatory use of alternative methods has still lagged behind. Critics have repeatedly pointed out that alternative test methods have not been accepted for regulatory decision making and that the expectations for real reductions in animal use in toxicology testing have always outpaced the documented progress. It has become clear that it is time to change our approach.

The NIEHS is beginning to move forward with a different philosophy toward ICCVAM. Rather than the NIEHS directing the activities of ICCVAM through NICEATM, the interagency agenda will now be driven by the partner regulatory agencies—the agencies that will ultimately implement the ICCVAM-recommended methods. Regulatory agencies are required by statute to use toxicology test information for a variety of purposes, including labeling and registration, and these requirements are not uniform. The ICCVAM Authorization Act acknowledges that some alternative test methods promoted by ICCVAM, while deemed valid, may not meet specific needs of a regulatory agency. With ICCVAM regulatory agencies taking ownership of the process, there should be a better match between the alternative test methods validated and the tests required to meet regulatory guidelines.

Toxicology testing is shifting from a primary focus on adverse phenotypic observations in animals to mechanism-based biological outcomes *in vitro*, and the NIEHS is embracing this paradigm shift through its participation in the multiagency Tox21 consortium (Collins et al. 2008). NICEATM will expand its scope and concentrate its resources on providing bioinformatic and computational toxicology support to NIEHS Tox21 projects.

With its purpose of transforming toxicology by shifting from *in vivo* animal studies to *in vitro* assays, *in vivo* assays in lower organisms, and computational modeling for toxicity assessments, Tox21 has the real potential to result in dramatic changes in the numbers and types of organisms used for toxicology testing. A stronger interface of NICEATM with Tox21 will better position ICCVAM for addressing how data from these new methods can be integrated into the existing regulatory framework.

We express our deep appreciation to William S. Stokes, who has served as the director of NICEATM since its inception. In December 2012, he retired from the Public Health Service after 33 years of dedicated federal service. His vision, persistence, and direction have been key to bringing NICEATM, ICCVAM, and the International Cooperation on Alternative Test Methods (ICATM) to their current stage of maturity.

We are pleased that Warren Casey, who has served as deputy director of NICEATM, will now serve as the acting director. He is uniquely qualified for this role, having worked in the areas of toxicogenomics, mechanistic toxicology, and biomarker development in the pharmaceutical industry prior to joining the NIEHS.

We look forward to this new approach to promoting the 3Rs—an approach that will be driven by regulatory agency needs while remaining responsive to the test method development community.

The author declares she has no actual or potential competing financial interests.

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Research Triangle Park, North Carolina
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References

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ICCVAM Authorization Act. 2000. Public Law 106-545. Available: http://www.gpo.gov/fdsys/pkg/PLAW-106publ545/pdf/PLAW-106publ545.pdf [accessed 10 January 2013].
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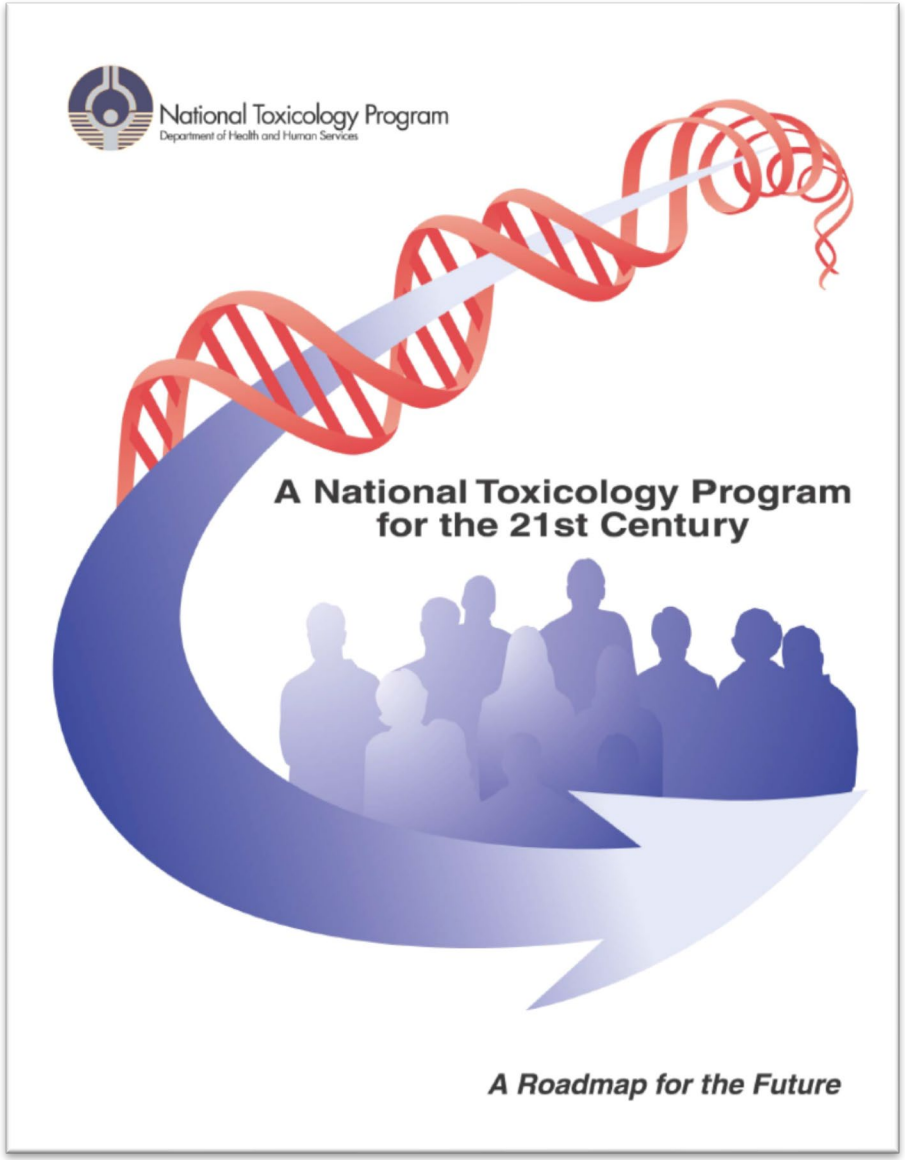
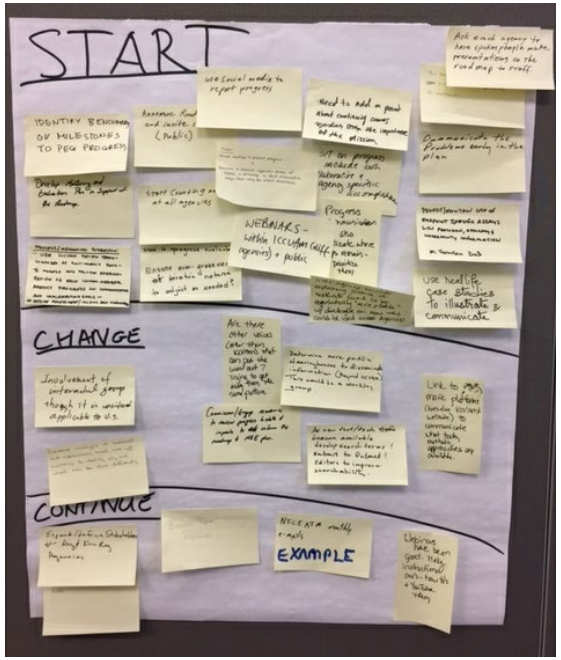


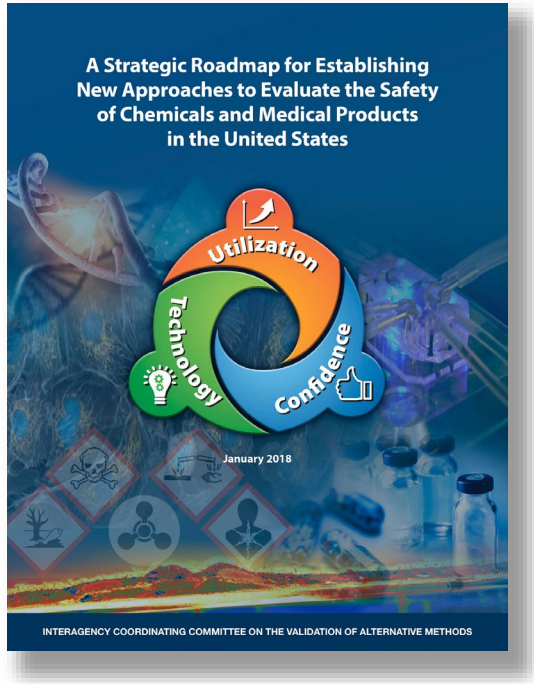
- **2004 NTP Roadmap:**
- The NTP Vision for the 21st Century:

  To support 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.

- **2007 NRC Report:**
- Calls for transforming toxicology: *"from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin."*
- Envisions pathway-based toxicology, where pathway perturbations are used to predict adverse effects
- **2009 NRC report**: *"the realization of the promise [of the 2007 report] is at least a decade away"*

U.S. Strategy and Roadmap: January 2018





- **Connect end users with the developers of alternative methods**
- **Establish new validation approaches that are more flexible and efficient**
- **Ensure adoption and use of new methods by both regulators and industry**

More information: https://ntp.niehs.nih.gov/go/natl-strategy

Implementation of the Roadmap

Where we are today…

THANK YOU!