20 Years of Scientific Accomplishments

Emily Reinke, Ph.D., DABT

September 2, 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

20 YEARS OF ICCVAM
Advancing Alternatives to Animal Testing

An ICCVAM Timeline

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

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

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

1997: Ad hoc committee recommends establishment of permanent ICCVAM Committee

2000: ICCVAM Authorization Act passed establishing 15-agency committee

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

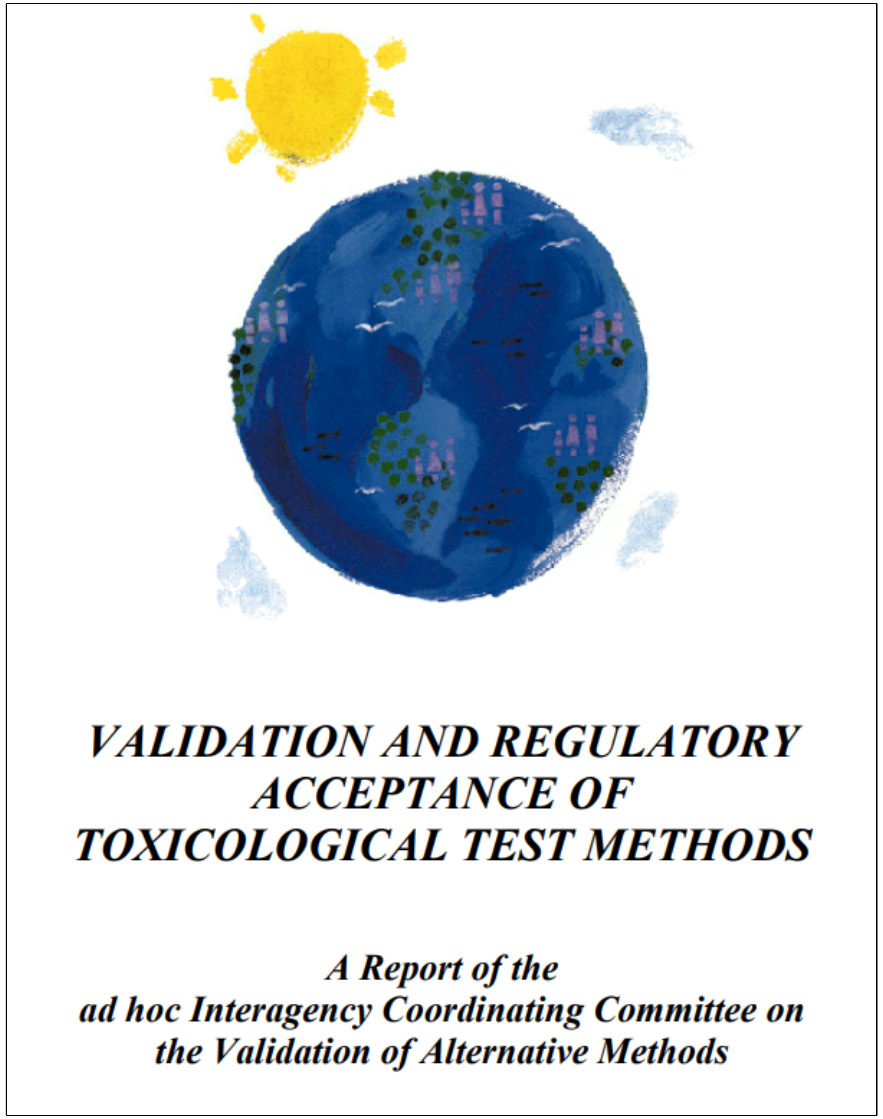
2014: First ICCVAM Public Forum

2015: First ICCVAM ICCVAM Communities of Practice webinar

2017: NIST joins ICCVAM

2018: U.S. Strategic Roadmap published

ICCVAM started as an ad hoc committee

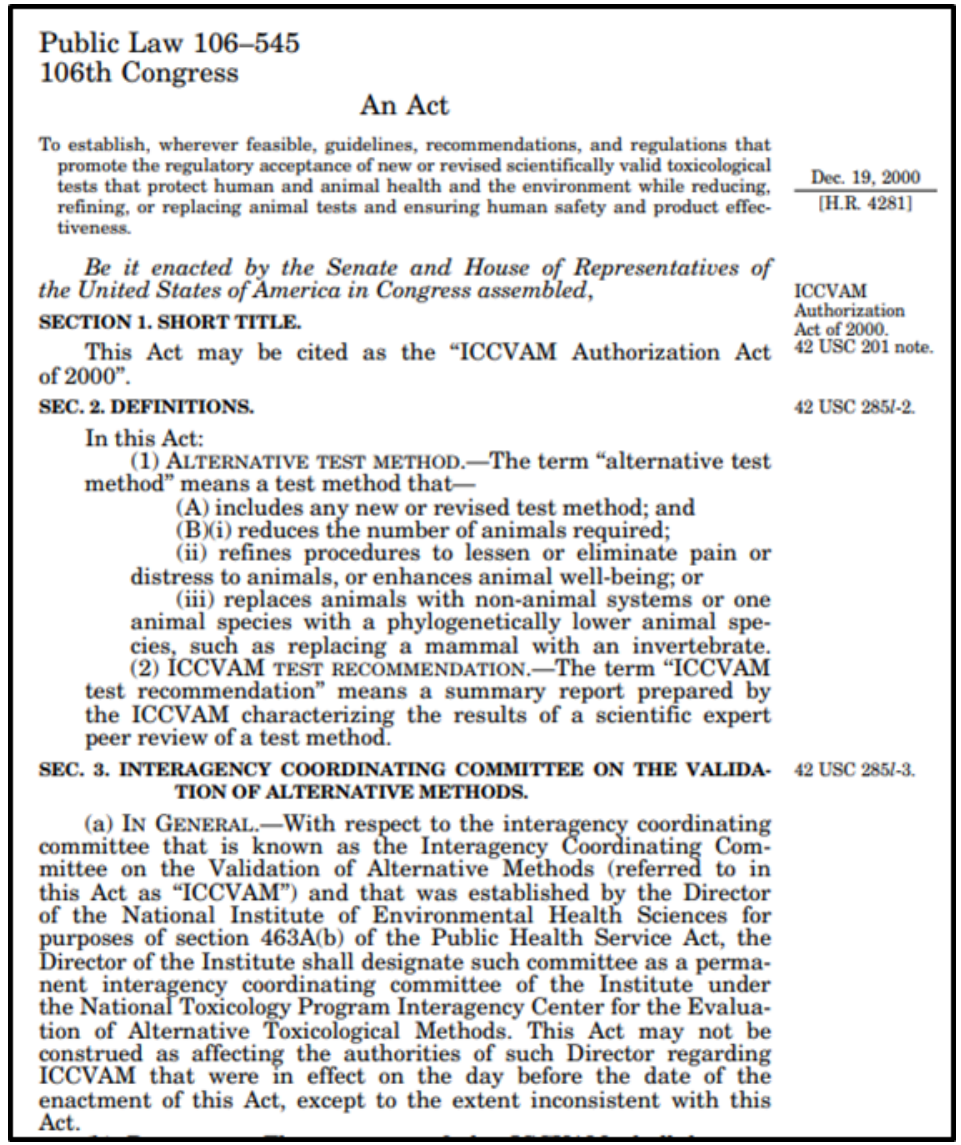


ICCVAM Authorization Act of 2000

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.

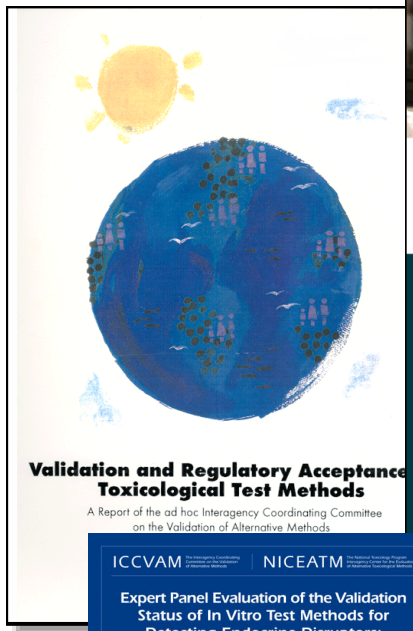
SEC. 3. INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS.

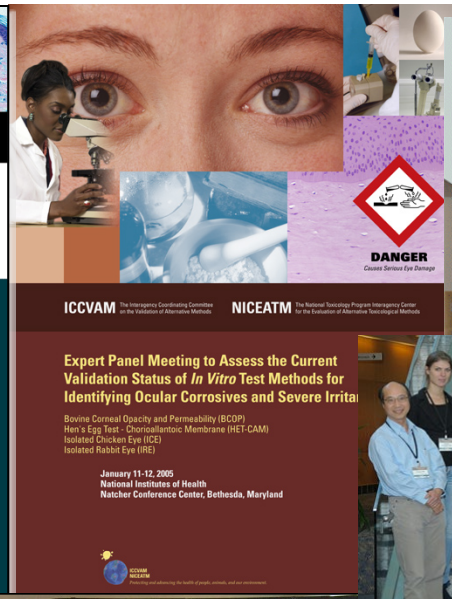
(a) IN GENERAL.—With respect to the interagency coordinating committee that is known as the Interagency Coordinating Committee on the Validation of Alternative Methods (referred to in this Act as "ICCVAM") and that was established by the Director of the National Institute of Environmental Health Sciences 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.

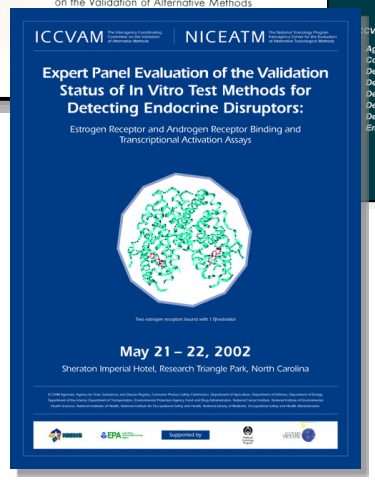
ICCVAM Workgroups and Subcommittees

- 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

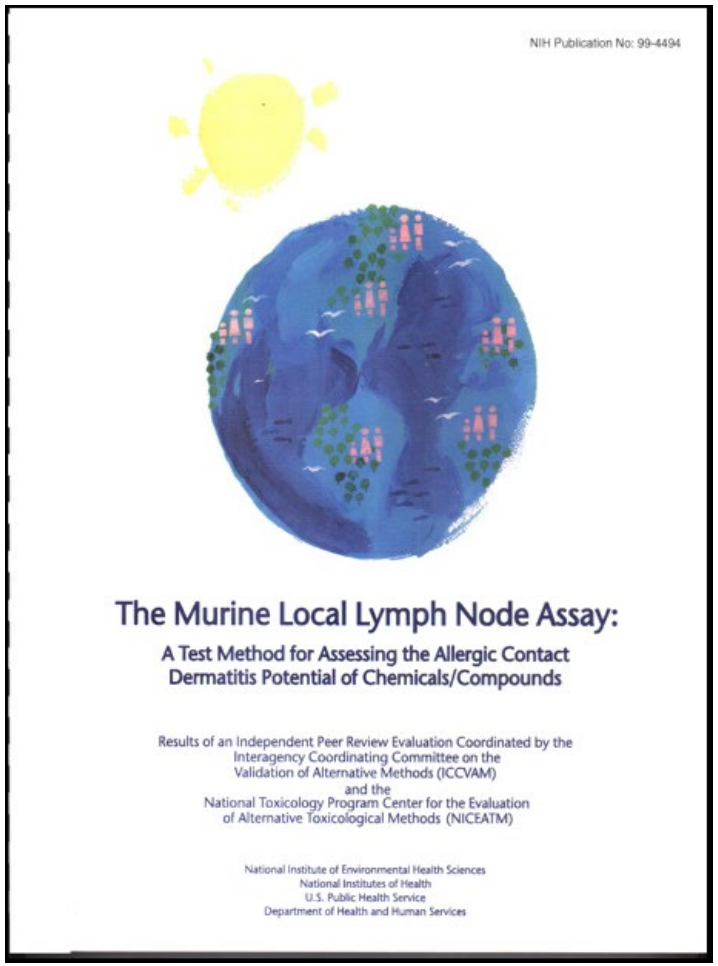
The first 10 years – Validation and Peer Review







The Local Lymph Node Assay: An ICCVAM First



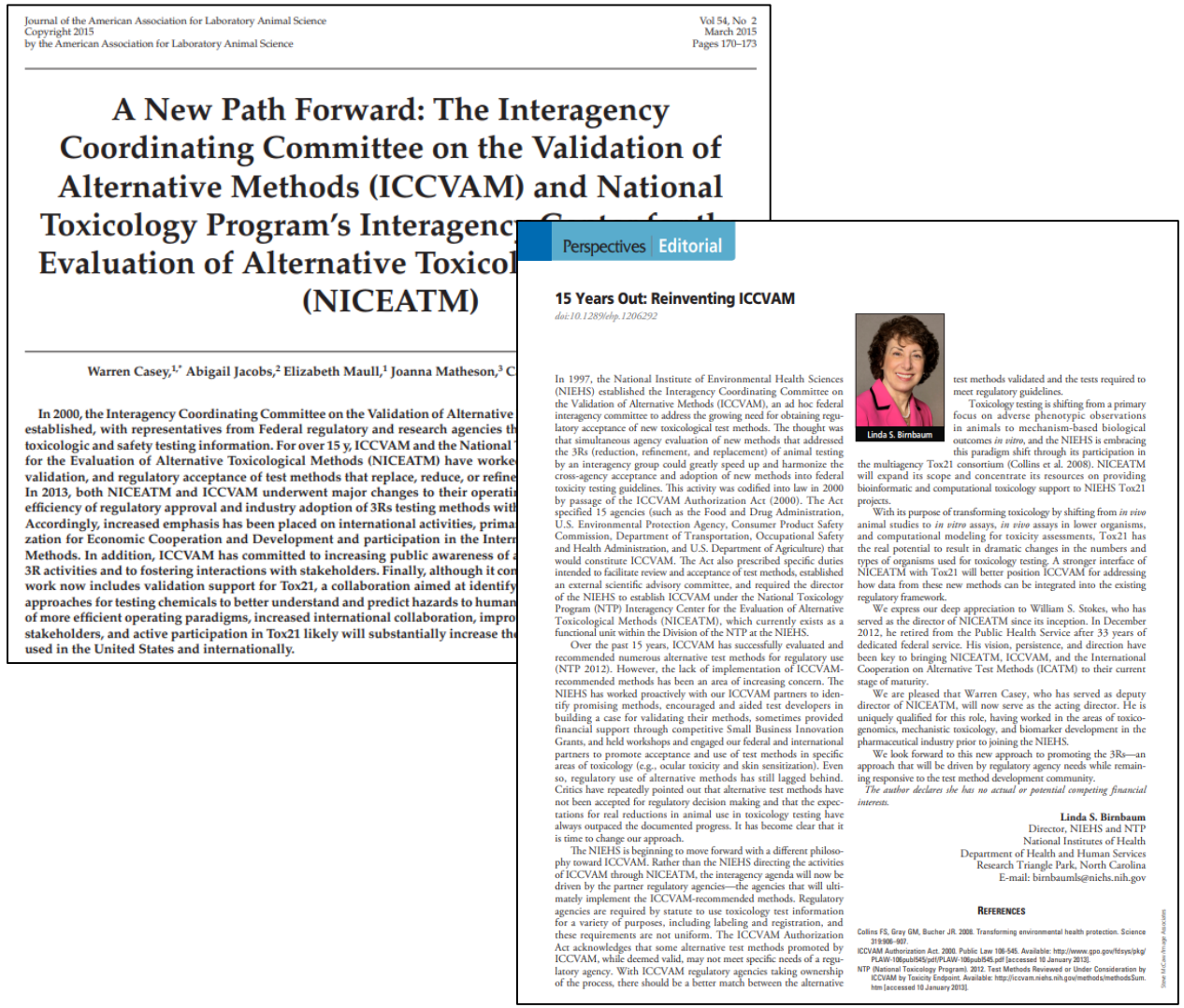
https://ntp.niehs.nih.gov/go/40482

- 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

- **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"*

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



Journal of the American Association for Laboratory Animal Science
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Vol 54, No 2
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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E-mail: birnbaumls@niehs.nih.gov

References

Collins FS, Gray GM, Bucher JR. 2008. Transforming environmental health protection. Science 319:906–907.
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].
NTP (National Toxicology Program). 2012. Test Methods Reviewed or Under Consideration by ICCVAM by Toxicity Endpoint. Available: http://iccvam.niehs.nih.gov/methods/methodsSum.htm [accessed 10 January 2013].

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)

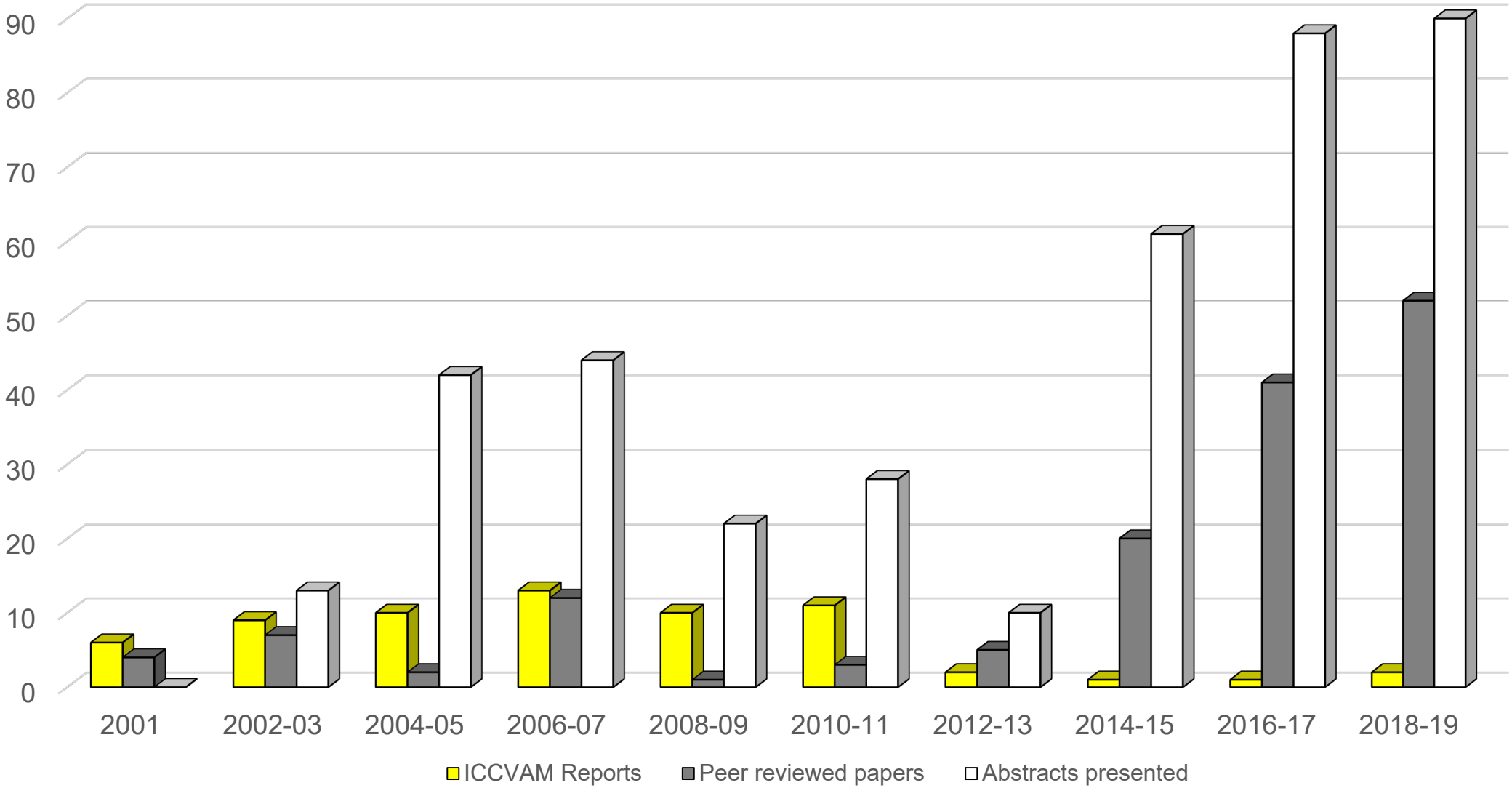
SOT | Society of Toxicology

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

SOT Achievement Award

- 2019: Nicole Kleinstreuer (former NICEATM Deputy, current Acting Director)

20 Years of Contributions: Publications and Presentations



ICCVAM Workshops – Presenting the State of the Science

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

Scientific Workshop on Alternative Methods to Refine, Reduce, and Replace the Mouse LD_{50} Assay for Botulinum Toxin Testing

November 13-14, 2006 | Crowne Plaza Hotel | Silver Spring, MD

ICCVAM Interagency Coordinating Committee on the Validation of Alternative Methods | NICEATM National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods | ECVAM European Centre for the Validation of Alternative Methods

International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning The Way Forward

October 11-13, 2011
U.S. Department of Agriculture
Center for Veterinary Biologics
National Centers for Animal Health
Ames, Iowa, USA

Organized by:
NICEATM - National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

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

Alternative Approaches for Identifying Acute Systemic Toxicity: Moving From Research to Regulatory Testing

September 24 – 25, 2015
9:00 a.m. – 5:00 p.m.
Porter Neuroscience Research Center
National Institutes of Health
Bethesda, Maryland

For agenda and registration information, visit
http://ntp.niehs.nih.gov/go/atwksp-2015

Individuals with disabilities who need accommodation to participate in this event should

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

In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making

WORKSHOP

Wednesday, February 17, 2016 • 8:00 a.m. – 6:00 p.m.
Thursday, February 18, 2016 • 8:30 a.m. – 3:00 p.m.
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina

For agenda and registration information, visit http://ntp.niehs.nih.gov/go/ivive-wksp-2016

Individuals with disabilities who need accommodation to participate in this event should contact Elizabeth Maull at 919-316-4668 or maull@niehs.nih.gov. TTY users should contact the Federal TTY Relay Service at 800-877-8339. Requests should be made at least 5 business days in advance of the event.

Any individual seeking access to the EPA campus will need to be prepared to **show a photo ID** (e.g., driver's license, or a company, government, or university ID) and **provide either a copy of this flyer or pertinent information about the seminar** (e.g., name of the speaker, host, or title of the seminar).

EPA United States Environmental Protection Agency

International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions

September 14-16, 2010
William H. Natcher Conference Center
National Institutes of Health
Bethesda, MD, USA

Organized by:
NICEATM - National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
ICCVAM - Interagency Coordinating Committee on the Validation of Alternative Methods
ECVAM - European Centre for the Validation of Alternative Methods
JaCVAM - Japanese Centre for the Validation of Alternative Methods
Health Canada

For more information and to register, please contact NICEATM:
http://iccvam.niehs.nih.gov | 919-541-2384 | niceatm@niehs.nih.gov

ICCVAM Agencies:
- Agency for Toxic Substances and Disease Registry
- Consumer Product Safety Commission
- Department of Agriculture
- Department of Defense
- Department of Energy
- Food and Drug Administration
- National Cancer Institute
- Department of Transportation
- National Institute for Occupational Safety and Health
- National Institute of Environmental Health Sciences
- NIH Office of the Director
- National Library of Medicine
- Department of the Interior
- Occupational Safety and Health Administration
- Environmental Protection Agency

NIEHS National Institute of Environmental Health Sciences | NTP National Toxicology Program

Sponsored by: SOT Society of Toxicology

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

Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements

WEBINAR SE

21st Century Testing

Dan Huh, Ph
University of Penn

Kelly BéruBé,
Cardiff Univer

Thursday, Sept. 8, 2016 • 11:

This webinar is the last in a se
that will be presented throug
Please visit http://ntp.niehs.nih.gov/go/inh

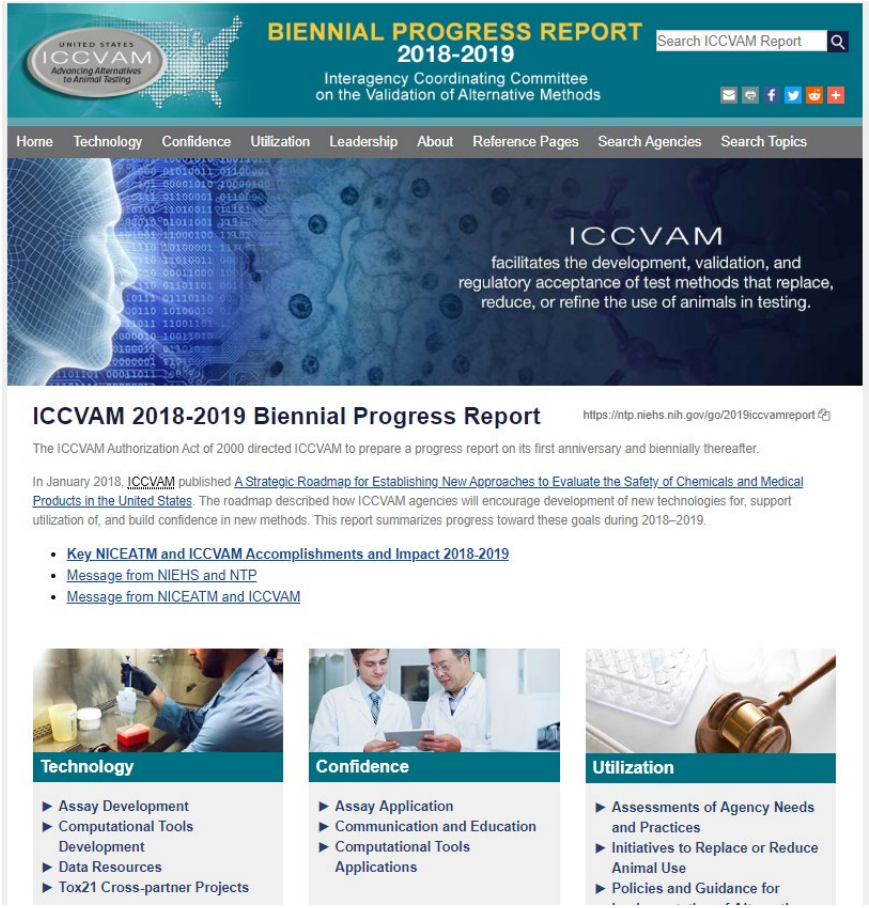
Scientific Workshop

Adverse Outcome Pathways: From Research to Regulation

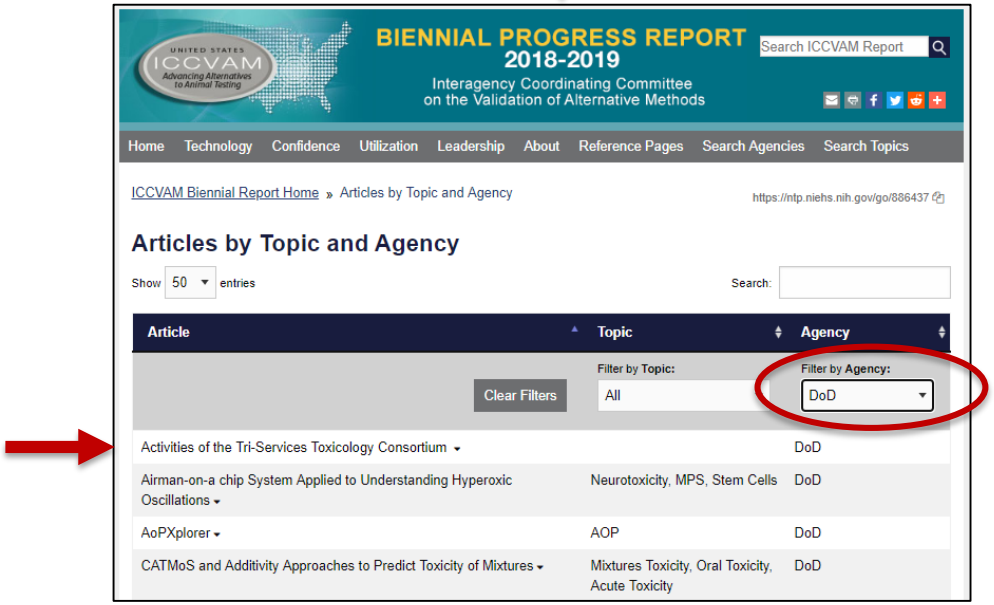
September 3-5, 2014

William H. Natcher
Conference Center
NIH, Bethesda, Maryland

ICCVAM Biennial Progress Report



- Required by the ICCVAM Authorization Act
- Summarizes agency activities to promote alternatives or reduce animal use
  - Contributions from every ICCVAM member agency
- 2018-2019 report published in July, available at https://ntp.niehs.nih.gov/go/2019iccvamreport



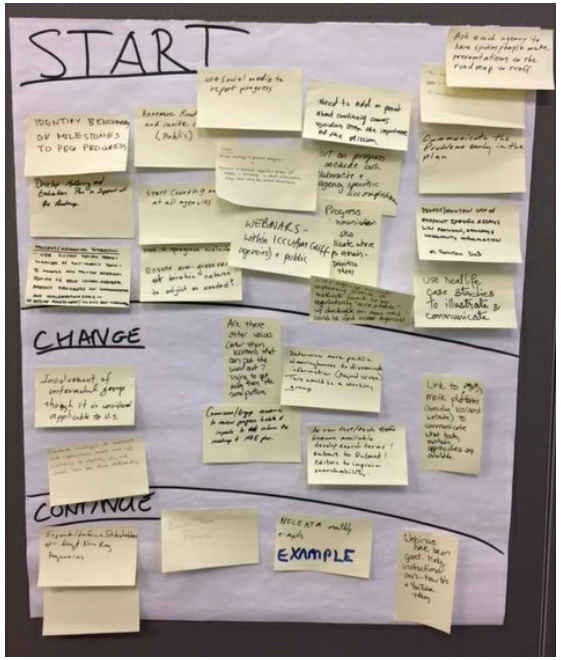
Biennial Report: Find Content by Agency

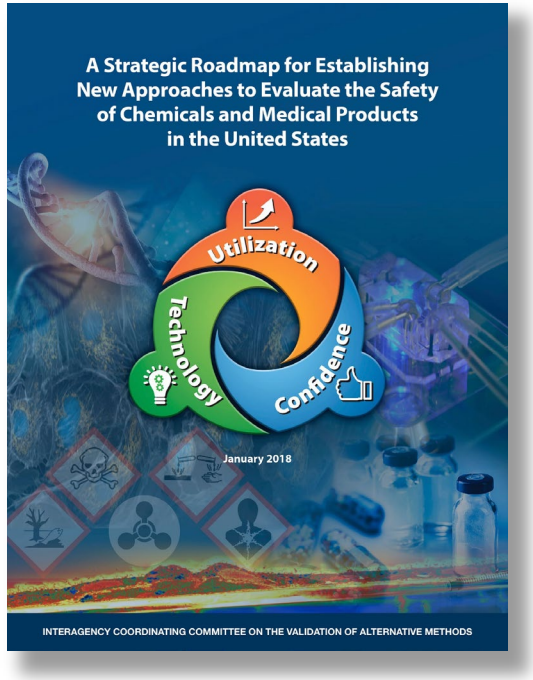
- Hover over “Search Agencies” to show a list of agencies
- Click on agency of interest
- List of articles tagged with that agency will come up
- Click on item to read article

Biennial Report: Find Content by Topic

- Hover over “Search Topics” to show a list of topics
- Click on topic of interest
- List of articles tagged with that topic will come up
- Click on item to read article

U.S. Strategy and Roadmap: January 2018



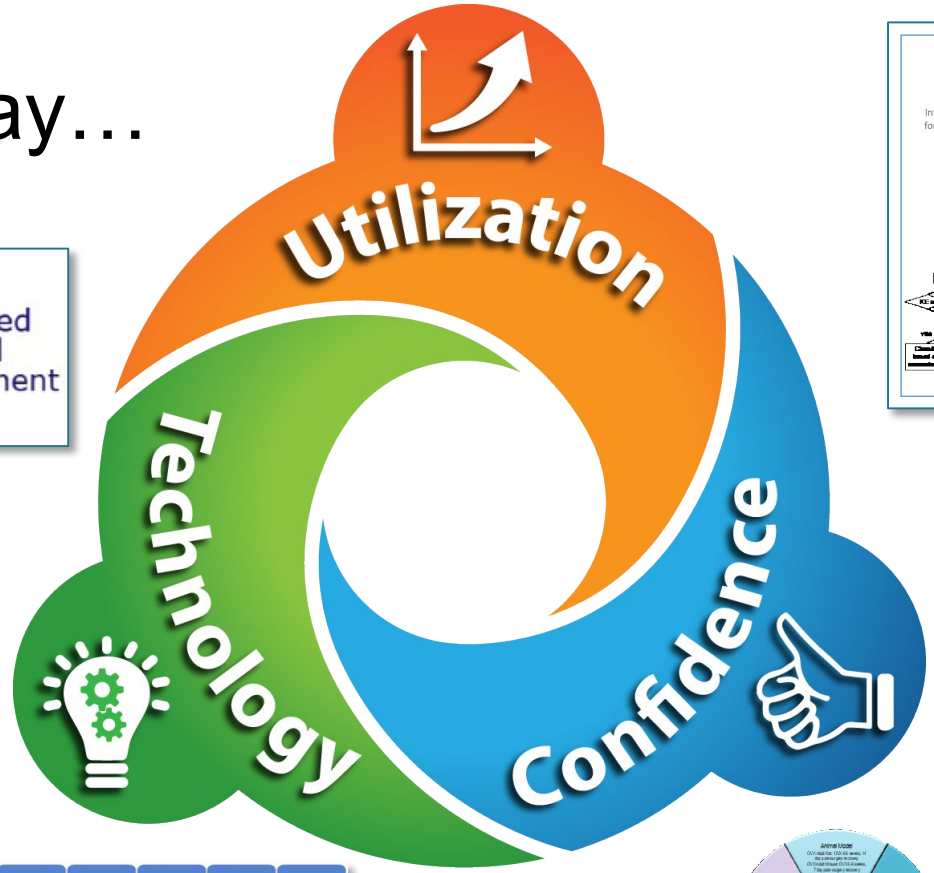


- **Connect end users with the developers of alternative methods**
- **Establish new validation approaches that are more flexible and efficient**
- **Ensure adoption and use of new methods by both regulators and industry**

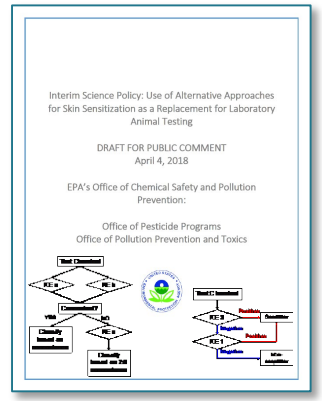
More information: https://ntp.niehs.nih.gov/go/natl-strategy

Implementation of the Roadmap

Where we are today…



Integrated Chemical Environment



CATMoS