NICEATM

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

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

Draft NICEATM-ICCVAM Five-Year Plan (2013-2017)

Joanna Matheson, PhD
Consumer Product Safety Commission
Subcommittee Chair

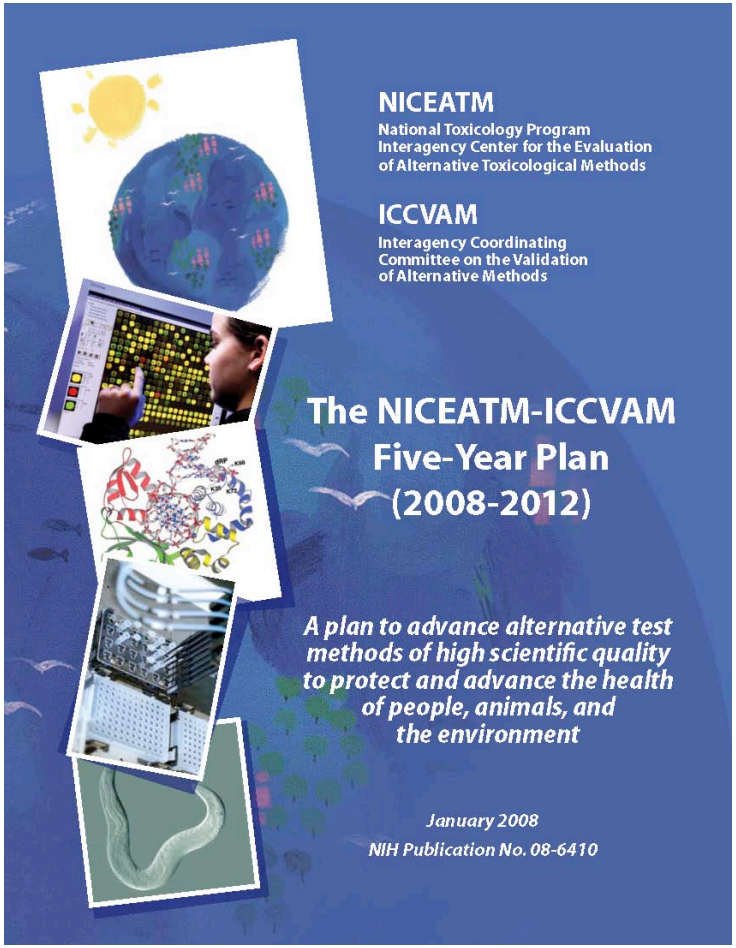
Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods

September 5, 2012

Research Triangle Park, NC

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

2008-2012 NICEATM-ICCVAM Five-Year Plan



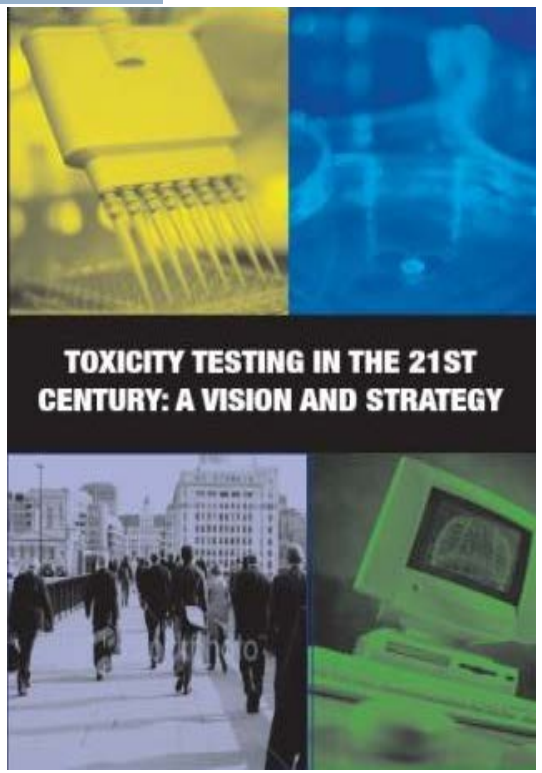
A plan to advance alternative test methods of high scientific quality to protect and advance the health of people, animals, and the environment

- Prepared in response to request from Congress to NIEHS
- NICEATM and ICCVAM partnered with relevant Federal agency program offices
- Details on execution of this strategic plan described in 2008 Implementation plan

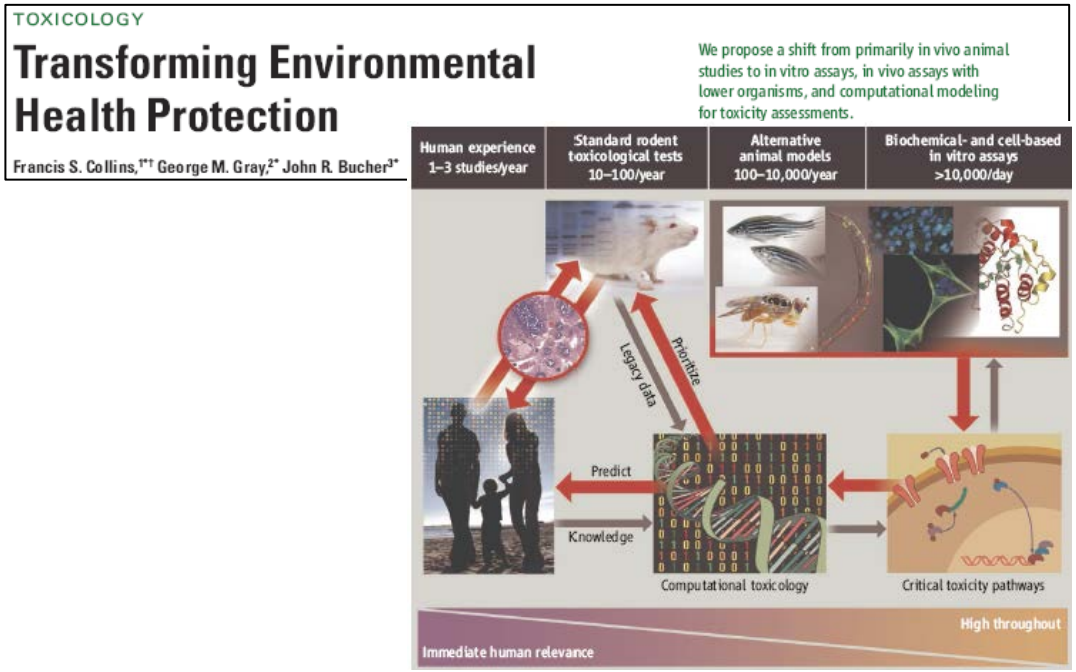
http://iccvam.niehs.nih.gov/docs/5yearplan.htm

Key Revisions to 2013-2017 NICEATM-ICCVAM Five-Year Plan

- Strategic plan emphasizes:
  - NICEATM and ICCVAM's role in the ongoing transformation of safety testing
  - 3Rs progress made during implementation of 2008-2012 Five Year Plan
  - Opportunities for additional 3Rs progress



National Research Council 2007



Science. 2008 Feb 15;319(5865):906-7.

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Phases for Drafting 2013-2017 NICEATM-ICCVAM Five-Year Plan

Phase 1

Prepare Draft Plan

- **November 2011**
  - Requests for input from ICCVAM agencies and public comments
- **April 2012**
  - ICCVAM approved Draft Plan for release to the public and SACATM for comment

Phase 2

Solicit comments on Draft Plan

- **June 2012**
  - FR notice announcing availability of Draft Plan for Public Comment
- **September 2012**
  - SACATM Meeting: SACATM and public comment on Draft Plan

Phase 3

Consider comments and finalize Plan

- **December 2012**
  - **Public Release of NICEATM-ICCVAM Five Year Plan**

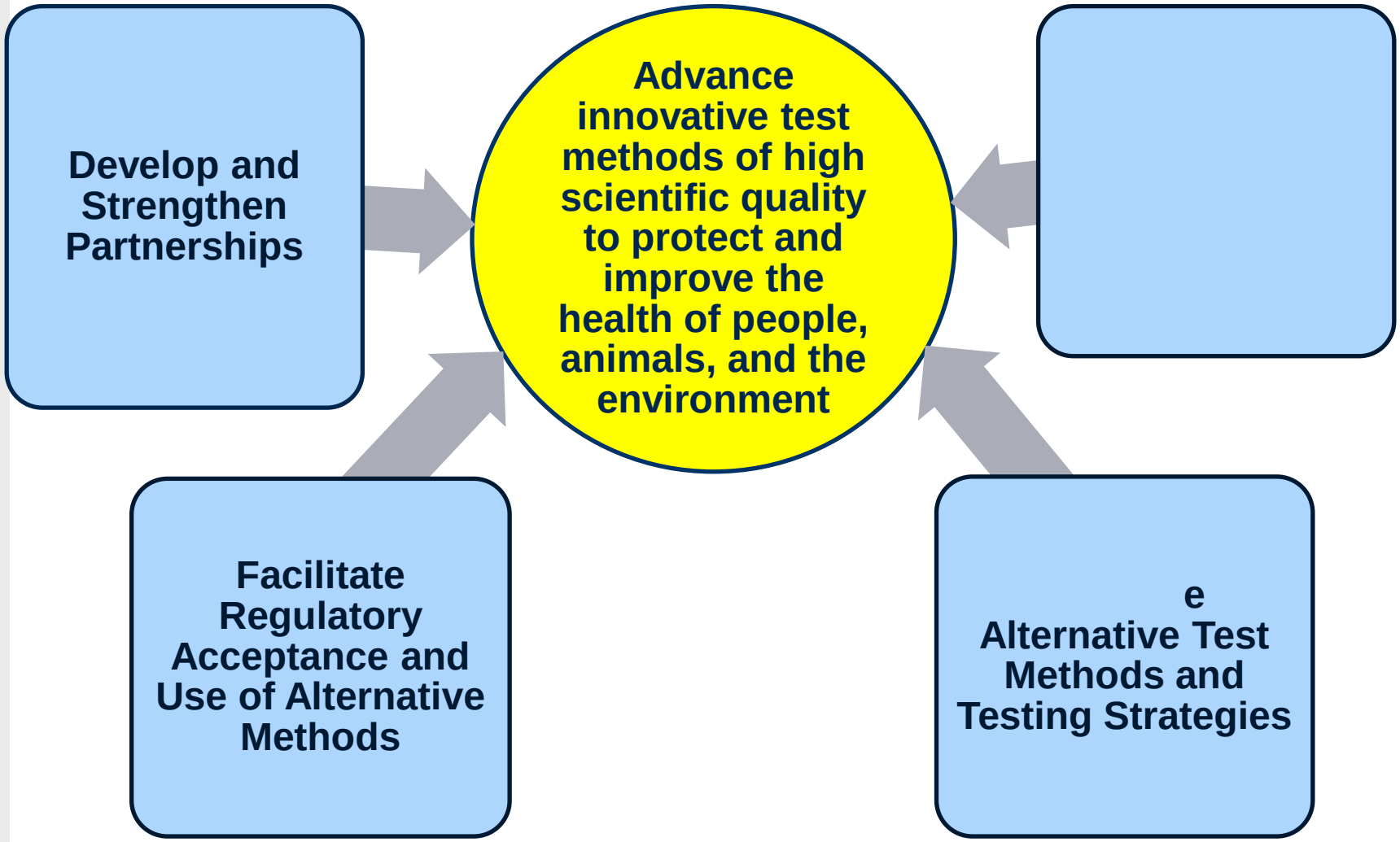
Draft Implementation Plan

2013-2017 NICEATM-ICCVAM Five-Year Plan

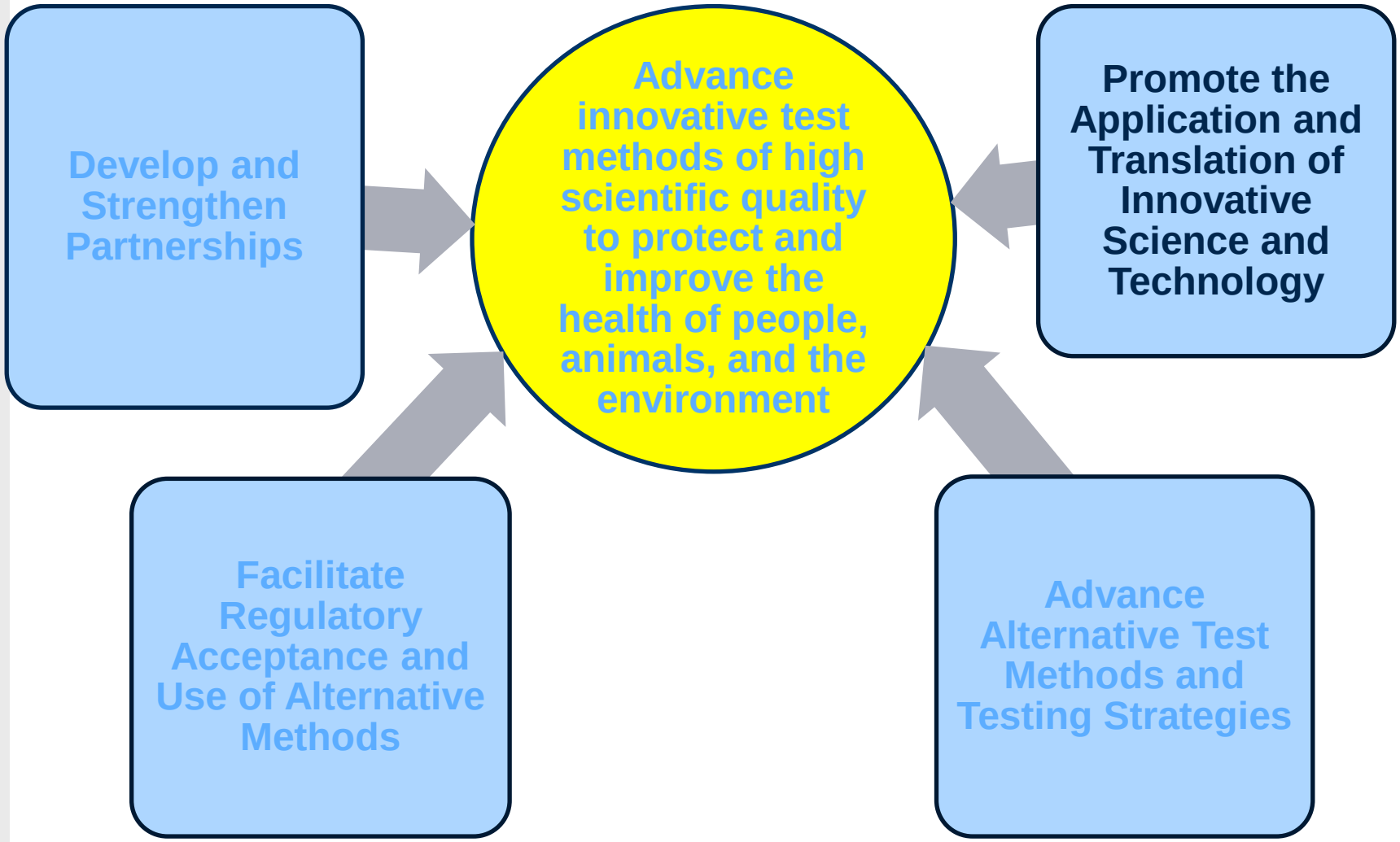
- 2013-2017 Five-Year Plan: Draft
  - Strategic document
  - Developed by ICCVAM members with stakeholder input from public and SACATM
  - Focuses on strategies to provide a basis for action
  - Template for organizing overall effort to develop, validate, and implement alternative safety testing methods
- 2013-2017 Implementation Plan: Under development
  - Working document
  - Will be drafted by ICCVAM members with input from ICCVAM Interagency Working Group members
  - Will detail specific goals, objectives, and progress in each strategic area
  - First draft after completion of 2013-2017 Five-Year Plan
  - Progress on implementation provided yearly at SACATM meetings

Source: NICEATM-ICCVAM Five-Year Plan (2013-2017) http://iccvam.niehs.nih.gov/docs/5yrPlan/2013-5YP-14May2012v2-draft.pdf

2013-2017 Five-Year Plan:
Four Key Strategic Opportunities:



2013-2017 Five-Year Plan:
Key Strategic Opportunity:



Strategic Opportunity: Promote the Application and Translation of Innovative Science and Technology

- Eleven of the fifteen ICCVAM Federal agencies have research and development programs
- Strategies and Objectives:
  - Promote research and new technologies expected to advance development of alternative methods
  - Monitor R & D efforts and identify opportunities for new biomarkers and systems
  - Facilitate evaluation of new methods and models that may have utility for regulatory testing
  - Facilitate reviews of usefulness and limitations of defined high-throughput screening approaches
- Development and translation efforts for new testing models typically require several years

Innovative Science and Technology: Federal Regulatory Science Initiatives

- NIH - FDA Regulatory Science Initiative
  - Accelerate development and use of new tools, standards and approaches to more effectively evaluate product safety, efficacy and quality
  - NIH Common Fund Grants
- National Center for Advancing Translational Sciences (NCATS):
  - Established by NIH to catalyze innovative methods and technologies to enhance development, **testing**, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions
  - Monitor grants expected to generate innovative testing methods and promote their standardization and validation

NCATS Catalyzing Innovation

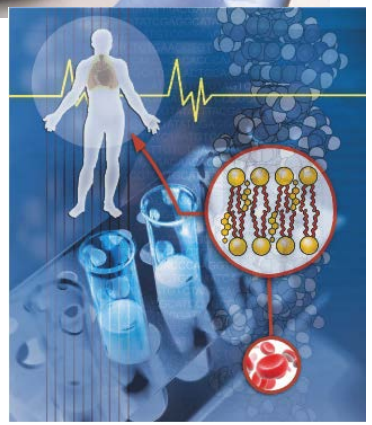
http://commonfund.nih.gov/regulatoryscience/fundedresearch.aspx

F.S. Collins. 2011. Reengineering Translational Science: The Time is Right, *Science Translational Medicine* 3(90):1-6

http://ncats.nih.gov/index.asp

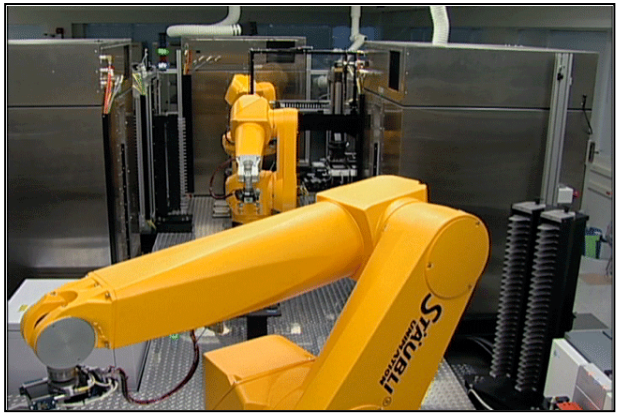
Innovative Science and Technology: Regulatory Science Opportunities for Next 5 Years

- Improved Test Models
  - High throughput microchip with multiple target organs
  - Stem cells
  - 3D cell cultures
  - Biological networks
  - “Omics”: genomics, proteomics, metabolomics
- High Throughput Screening and High Content Analyses
- Computational Models and Informatics
- Integrated Testing and Decision Strategies
- Biomarkers of Toxicity
- Innovative Approaches to Validation
  - Technical, biological, and regulatory validation
  - Validation of HTS methods and other innovative testing paradigms
  - Increased efficiency using performance standards



Innovative Science and Technology: Continued Progress in Regulatory Science

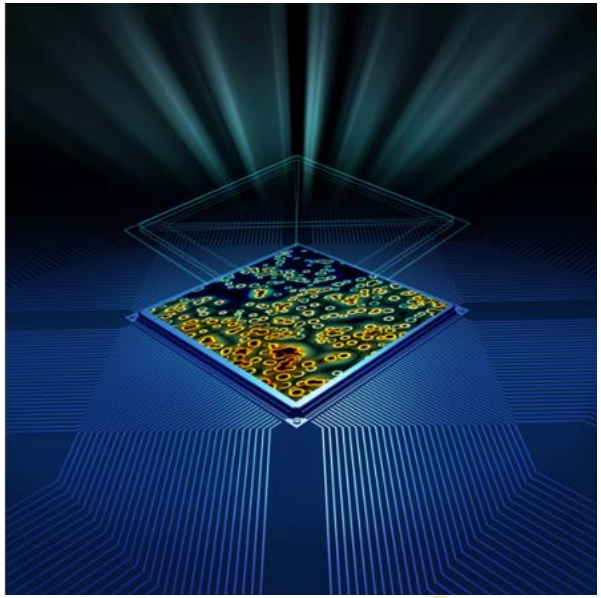
- Tox21: NICEATM and ICCVAM agencies participating in interagency collaboration between NTP, EPA, NIH NCATS, and FDA
  - Characterize toxicity pathways
  - Identify *in vitro* models/biomarkers predictive of biological responses
  - 2009: NICEATM nominated nearly 1000 chemicals for 10,000-chemical library used to evaluate each *in vitro* assay nominated and accepted for this initiative.



http://iccvam.niehs.nih.gov/docs/annrpt/BiennialRpt2010-508r.pdf

Innovative Science and Technology: Regulatory Science Opportunities for Next 5 Years

- Tissue Chip for Drug Screening Initiative
  - Interagency collaboration launched by NCATS in partnership with DARPA and FDA
  - Develop 3-D human tissue chips that accurately model structure and function of humans organs (lung, liver, heart) to predict the safety of potential drugs more swiftly and efficiently than current methods
  - 17 NIH award recipients
  - 2 DARPA cooperative agreements with the Wyss Institute at Harvard University and MIT to develop engineering platforms capable of integrating 10 or more organ systems



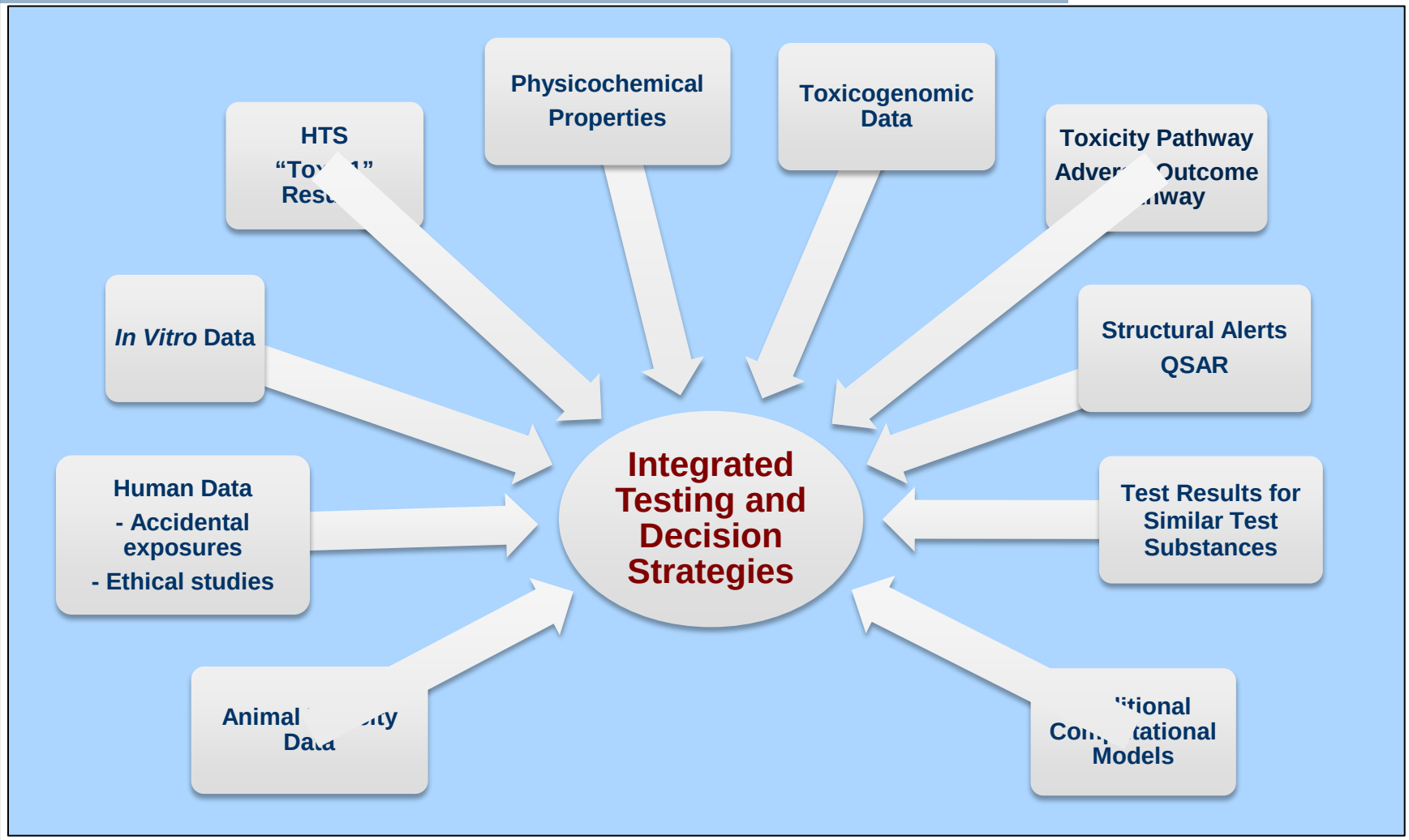
http://www.nih.gov/news/health/jul2012/ncats-24.htm

Innovative Science and Technology: Regulatory Science Opportunities for Next 5 Years

- EDSP21: Endocrine Disruptor Screening Program for the 21st Century
  - Use *in silico* models and *in vitro* high-throughput (HTP) assays to prioritize and screen chemicals for potential to interact with estrogen, androgen, or thyroid hormone systems
  - EPA proposes full replacement of current Tier 1 EDSP
    - 6,000 to 9,700 Chemicals for Prioritization and Screening
    - Cost > $1 million per chemical
    - Eleven test methods – six that use animals
    - A minimum of 492 animals used per chemical

http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf

Incorporate Innovative Science and Technology: Integrated Testing and Decision Strategies (ITDS)



Source: Adapted from Stokes WS, Wind M. 2010. Validation of innovative technologies and strategies for regulatory safety assessment methods: challenges and opportunities. *ALTEX* 27:87-95.

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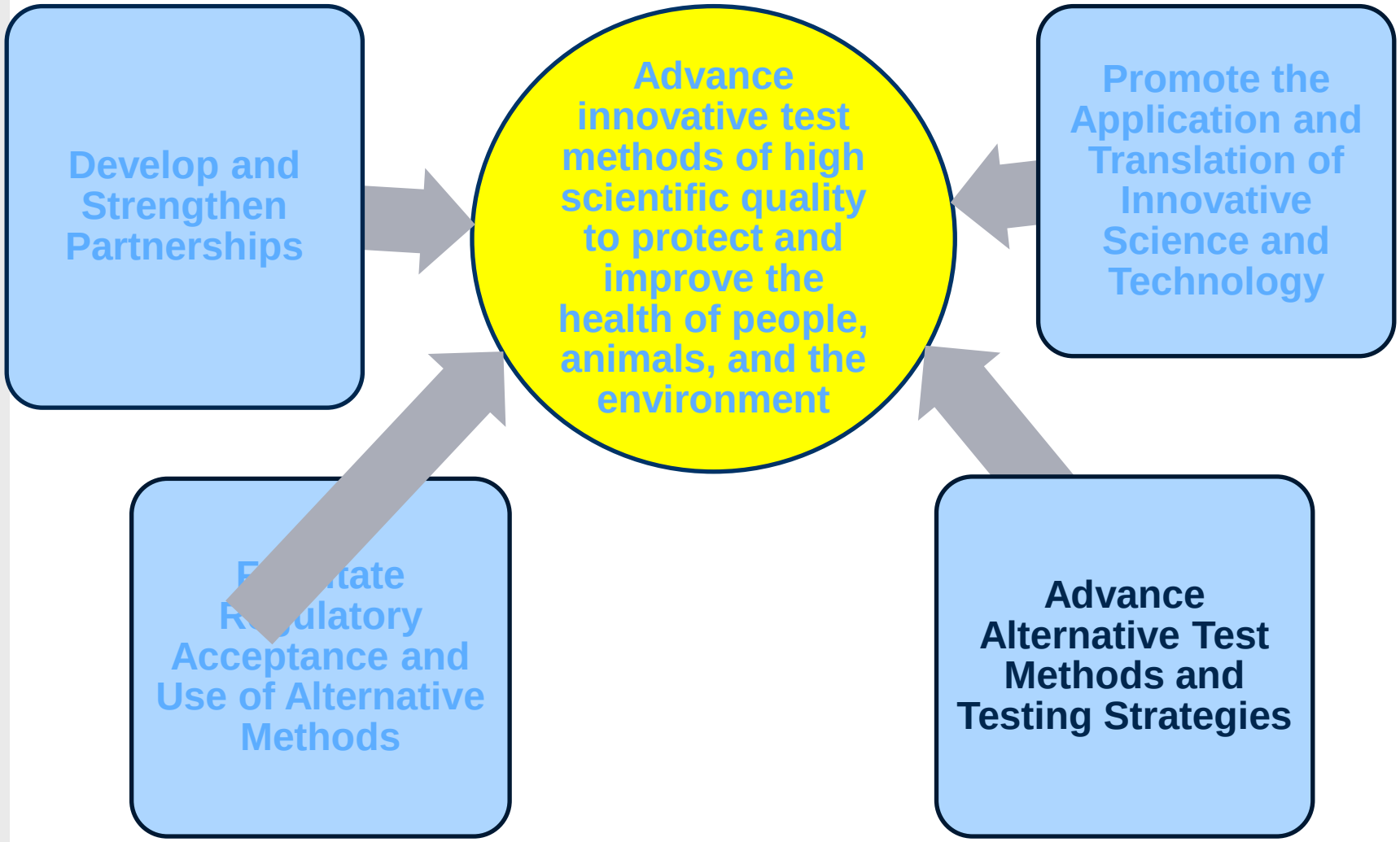
2013-2017 Five-Year Plan:
Key Strategic Opportunity:

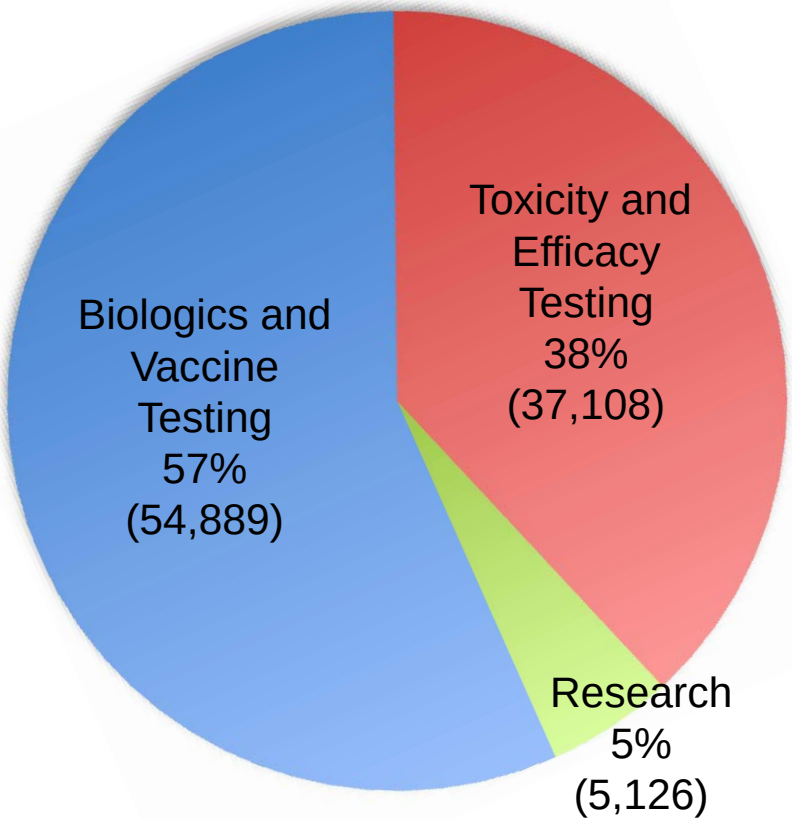


Strategic Opportunity: Advance Alternative Test Methods and Testing Strategies

- ICCVAM test method prioritization criteria
  1. Potential impact to:
     - **Replace** animal use
     - **Reduce** the number of animals used
     - **Refine** animal use to reduce or avoid unrelieved pain and distress, or otherwise improve animal welfare
  2. Applicable to needs and requirements of Federal Agencies
  3. Potential to improve prediction of adverse health or environmental effects
- Priorities may vary across Agencies
- Priorities may change
  - Need to be flexible to take advantage of advances in science and technology and availability of new methods

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

Animals by Testing Type Reported to USDA (2010):



- 95% (91,997) of the animals reported to USDA that experience unrelieved pain and distress are used for testing
- Including rats, mice, and birds, it is estimated that 2 million animals used for testing involves unrelieved pain and distress (U.S.)

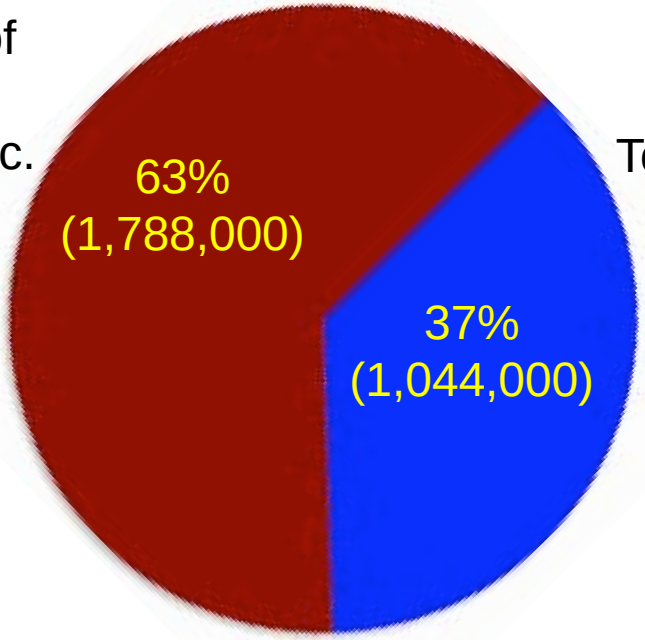
Data for all states [illegible]mal data for Column E of APHIS Form 7023; USDA. 2010. Annual Report - Animal Usage by Fiscal Year. United States Department of Agriculture. Animal and Plant Health Inspection Service. Available at: http://www.aphis.usda.gov/animal_welfare/efoia/7023.shtml

Based on NICEATM review of Column E justifications posted by USDA.

Animals Used for Testing by Major Categories

Vast Majority of Animal Use for Testing Biologics and Vaccines

Production and QC of Medicines, Biologics, Vaccines etc.



Toxicity Testing

Total 2010 EU annual animal use for testing: 2,832,000

Report on the Statistics on the Number of Animals used for Experimental and other Scientific Purposes in the Member States of the European Union COM(2010) 511

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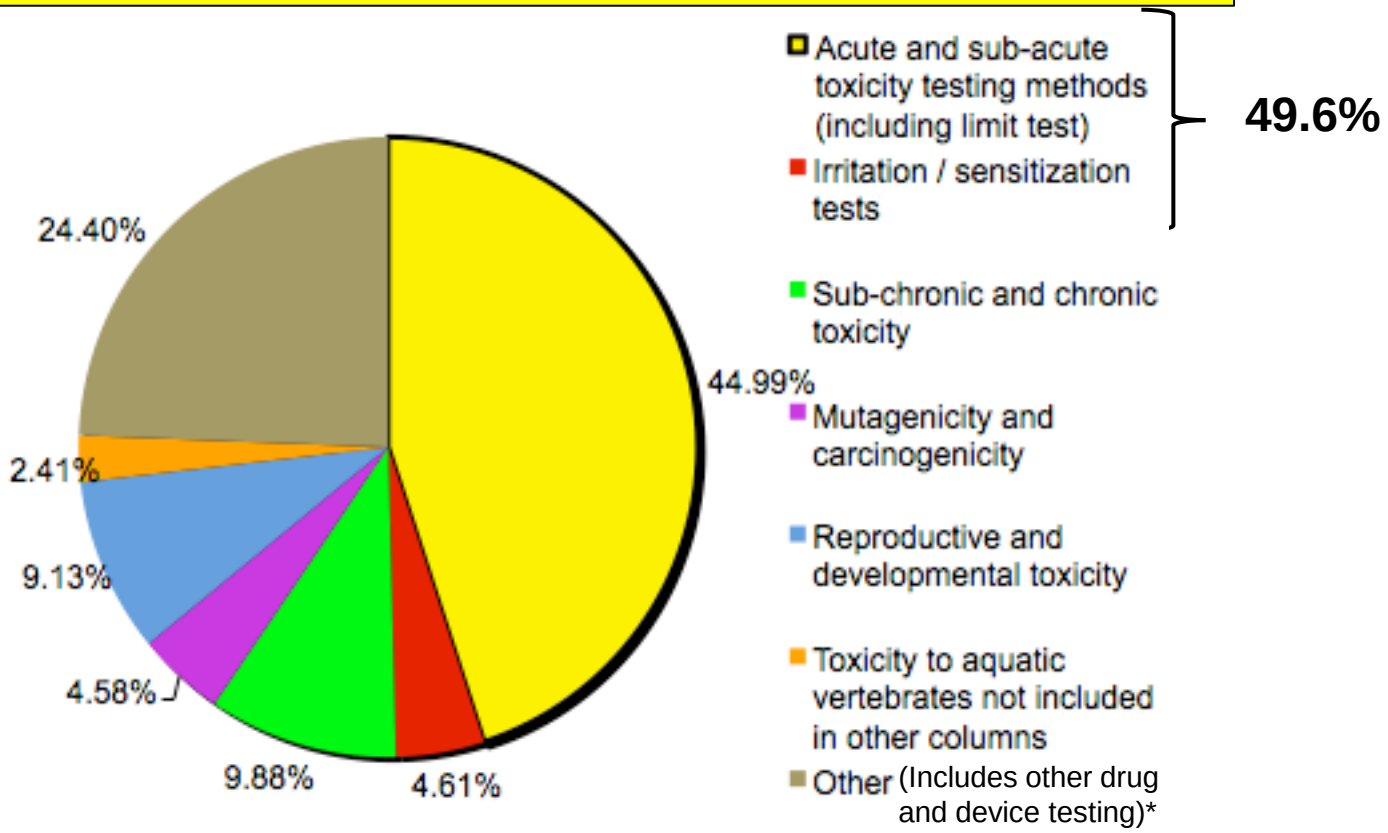
Animals Used for Toxicity Testing by Test Type

Half of Animals Used for Acute Systemic and Irritation/Sensitization Testing "Six Pack Tests"



*Other = "biological screening for pharmaceutical, healthcare and veterinary products, including neurotoxicity, toxicokinetics, testing of biological evaluation of medical devices"

Report on the Statistics on the Number of Animals used for Experimental and other Scientific Purposes in the Member States of the European Union COM(2010) 511

Strategic Opportunity: Advance Alternative Test Methods and Testing Strategies: Priorities

- Highest Priority Areas
  - Vaccines and Other Biologics
  - Acute Systemic Toxicity: Oral, Dermal, Inhalation
  - Ocular Toxicity
  - Dermal Toxicity
    - Acute Contact Dermatitis
    - Skin Irritation / Corrosivity
- Additional Priority Areas
  - Endocrine Disrupter Testing
  - Reproductive and Developmental Toxicity
  - Repeat Dose and Chronic Toxicity/Carcinogenicity Testing
  - Pyrogen Testing
  - Other Toxicity Areas

These priorities will evolve in response to new testing needs and scientific and technological advances

Strategic Opportunity: Advance Alternative Test Methods and Testing Strategies:

- Two major types of activities
  - Test method evaluations
  - State of the science workshops

Advance Alternative Test Methods and Strategies: Vaccines and Biologics

- Rationale for Priority
  - Accounts for at least 60% of animal use in testing
  - Accounts for majority of unrelieved pain and distress

- Applicable to Multiple Federal Agencies
  - HHS: FDA, CDC, NIH-NIAID, BARDA
  - USDA, DHS, DOD, DOI

- Public Health Significance
  - Biologics include vaccines, blood and blood components, tissues, antibodies, and other substances used to treat or protect against disease in humans and animals

http://iccvam.niehs.nih.gov/docs/5yrPlan/NICEATM5YR-Final.pdf

Advance Alternative Test Methods and Strategies: Vaccines and Biologics: Recent Milestones

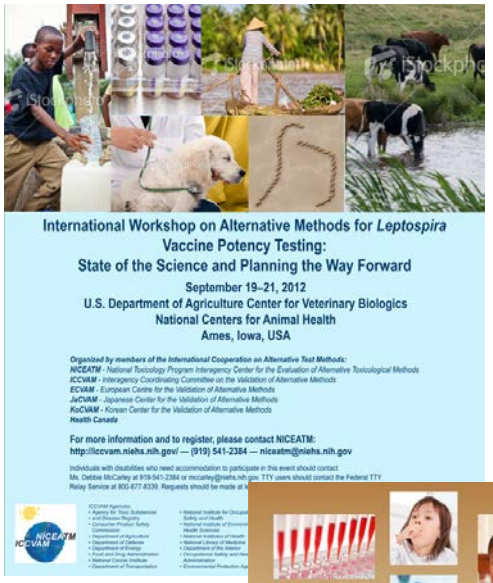
- September 2010 Vaccine Workshop identified priority areas for future vaccine workshops:
  - Rabies (2011)
  - Leptospirosis (2012)
  - Pertussis vaccines (2012)
  - Diphtheria and tetanus toxoids (2013)

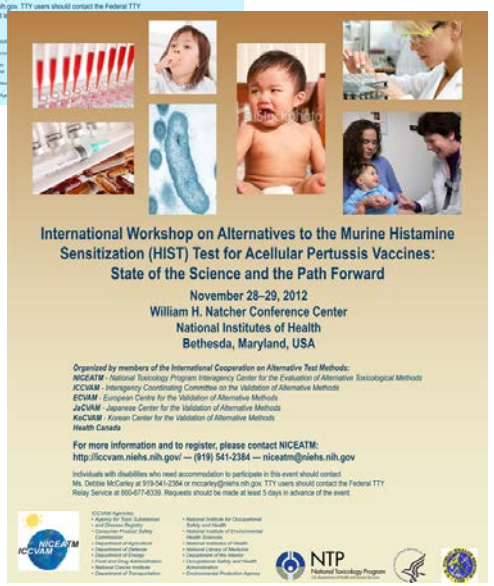
- October 2011 Rabies Vaccine Workshop identified areas for replacement, reduction, and refinement for human and veterinary rabies vaccines

- Agenda item tomorrow

Advance Alternative Test Methods and Strategies: Vaccines and Biologics: Ongoing Progress

- September 2012: *International Workshop on Leptospira Vaccine Potency Testing*
  - Develop 3Rs implementation strategy and plan to address identified knowledge and data gaps
- November 2012: *International Workshop on Alternatives to Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines*
  - Review of in vitro safety data on spiked Pertussis toxin vaccine preparations
- Agenda item tomorrow
- 3 *In Vitro* Assays that Detect and Quantify Botulinum Neurotoxin Serotypes
  - "High priority" by SACATM and ICCVAM
  - ICCVAM Botulinum Toxin Working Group (BTWG) - Advise on validation





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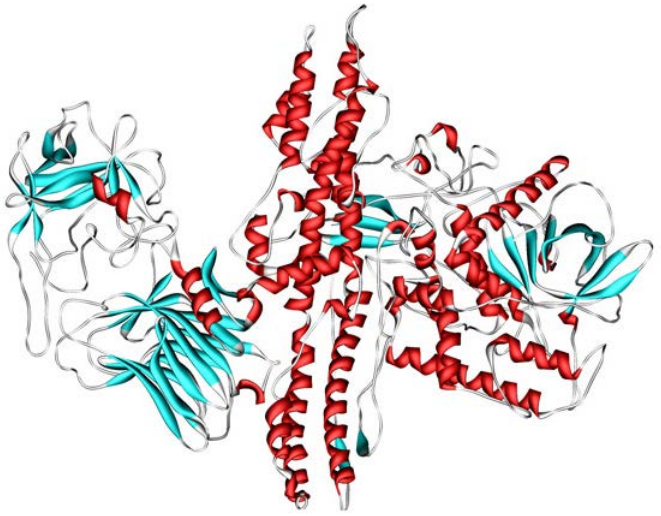
Advance Alternative Test Methods and Strategies: Vaccines and Biologics:

- Carry-over Activities Include:
  - Convene international workshop to review currently available alternative methods for BoNT detection and quantification to meet Federal agency needs
  - Convene international workshops in priority areas for alternative methods for human and veterinary vaccines
    - Diphtheria and Tetanus toxoids
    - Clostridial vaccines



Advance Alternative Test Methods and Strategies: Acute Systemic Toxicity

- Rationale for Priority
  - Accounts for more animal use than any other toxicity testing
  - Involves significant unrelieved pain and distress
  - Most commonly conducted product safety tests worldwide
- Applicable to Multiple Federal Agencies
  - HHS: FDA, NIH-NIEHS
  - ATSDR, CPSC, DOD, DOT, EPA, NIOSH, OSHA
- Public Health Significance
  - In 2010: 2,384,825 human poisonings reported, resulting in 1146 fatalities
  - Potential poisons must be accurately identified to adequately protect human and animal health, and determine appropriate use of child-resistant packaging

http://iccvam.niehs.nih.gov/docs/5yrPlan/NICEATM5YR-Final.pdf
http://www.aapcc.org/dnn/Portals/0/2010%20NPDS%20Annual%20Report.pdf
http://www.cdc.gov/injury/wisqars

Advance Alternative Test Methods and Strategies: Acute Systemic Toxicity: Recent Milestones

- 2008: ICCVAM Recommendations to *in vitro* basal cytotoxicity test methods to estimate starting doses for acute oral systemic toxicity testing
  - Potential to reduce animal use per test by an additional 50%
  - 2010: Adoption of OECD Guidance Document 129
    - Provides guidance on *in vitro* cytotoxicity tests used to set starting doses for acute oral systemic toxicity tests
- 2009: Updated OECD TG 403: Acute Inhalation Toxicity and Adopted TG 436: Inhalation Toxicity - acute toxic class method
  - Reduced animals used per test

http://iccvam.niehs.nih.-ov/docs/annrpt/BiennialRpt2010-508r.pdf
http://iccvam.niehs.nih.gov/docs/annrpt/Biennial2012-508.pdf

Advance Alternative Test Methods and Strategies: Acute Systemic Toxicity:

Carry-over Activities Include

- Develop, evaluate, and recommend a dermal up-and-down procedure (UDP) with the potential to reduce animal use by up to 85%
- Establish database containing high quality data from federal agencies to facilitate replacement strategies
- Continue collaborating with EURL-ECVAM to complete the validation of a stable liver cell model applicable to acute systemic toxicity testing and achieve adoption of OECD test guideline

Advance Alternative Test Methods and Strategies: Ocular Toxicity

- Rationale for Priority
  - One of the four most commonly required product safety tests worldwide
  - Rabbits used to identify ocular hazards can experience significant pain and distress during test article application when eye injuries occur
  - Required by multiple regulatory agencies
- Applicable to Multiple Federal Agencies
  - EPA, CPSC, FDA
- Public Health Significance
  - Appropriate identification of hazards necessary to help prevent eye injuries
  - Substances that may cause temporary or permanent damage to the eyes must be appropriately packaged, labeled, and handled to prevent exposures that may result in injuries

http://iccvam.niehs.nih.gov/docs/5yrPlan/NICEATM5YR-Final.pdf

Advance Alternative Test Methods and Strategies: Ocular Toxicity: Recent Milestones

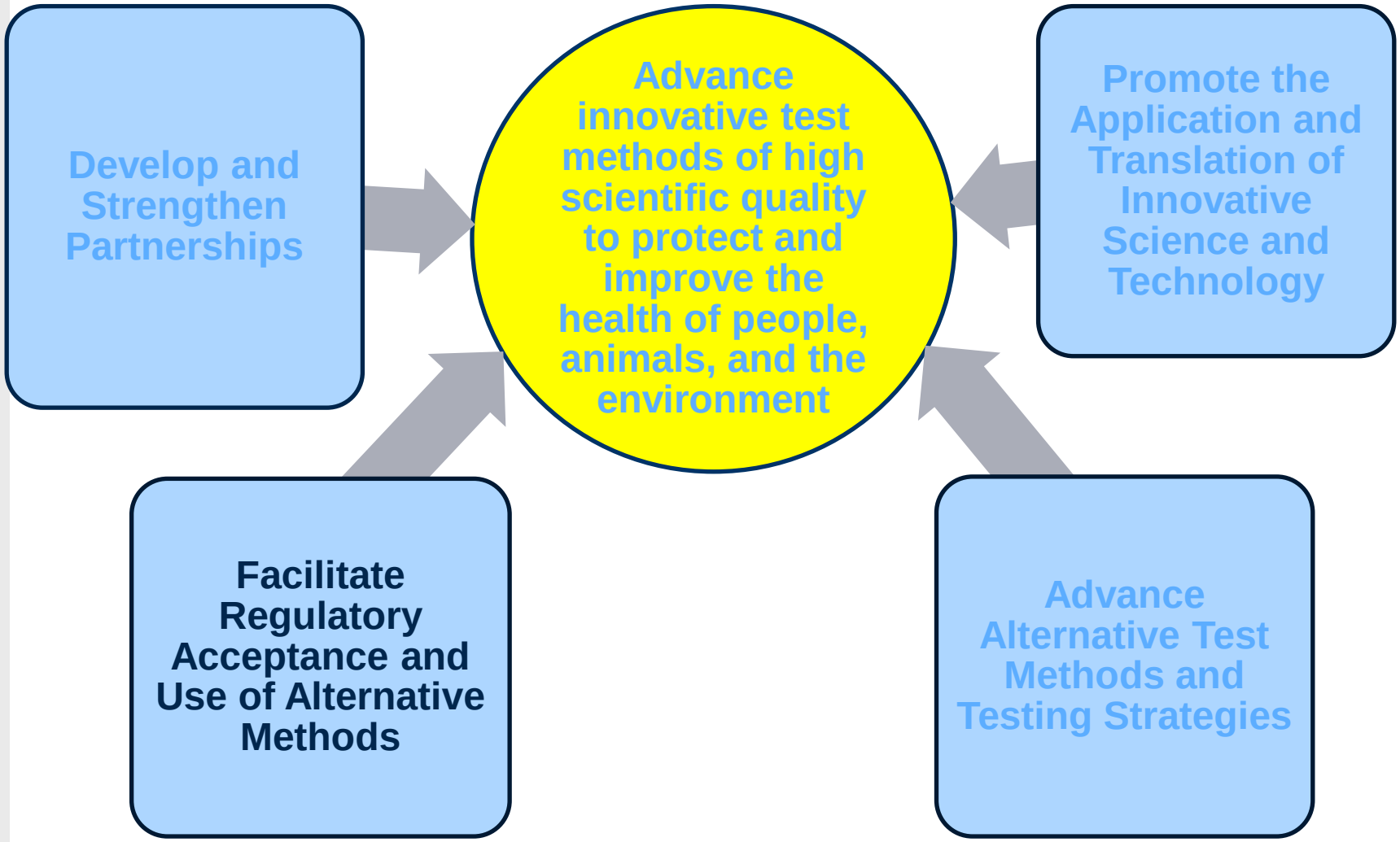
- Replacement (some testing situations): Available and approved / recommended non-animal test methods
  - Bovine corneal opacity and permeability (BCOP)
  - Cytosensor® Microphysiometer (CM)
  - Fluorescein Leakage (FL)
  - Isolated chicken eye
- Reduction: Strategies to minimize numbers
  - 1990: 6 to 18 animals per test; no *in vitro* methods
  - 2012: 0 to 3 animals; 4 *in vitro* test methods
- Refinement: Pain management procedures that should *always* be used when it it is determined necessary to perform rabbit eye test

Advance Alternative Test Methods and Strategies: Ocular Toxicity:

Carry-over Activities Include

- Evaluate validation status of Short Term Exposure (STE) and Isolated Rabbit Eye (IRE) tests
- Develop a recommended substance list for testing all ocular hazard categories for alternative methods and ITDS
- Contribute to development of AOP for eye injury in conjunction with international partners

2013-2017 Five-Year Plan:
Key Strategic Opportunity:



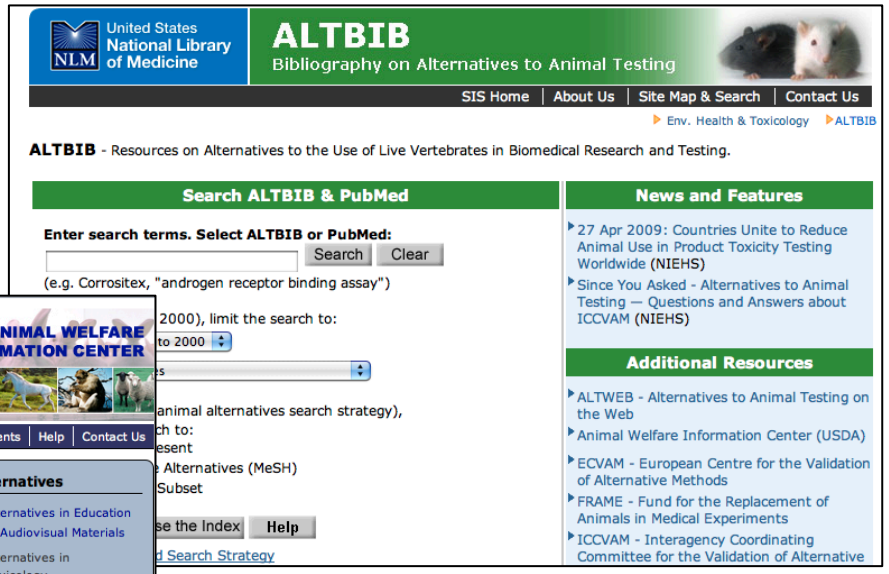
Strategic Opportunity:
Promote Regulatory Acceptance and Use of Alternatives

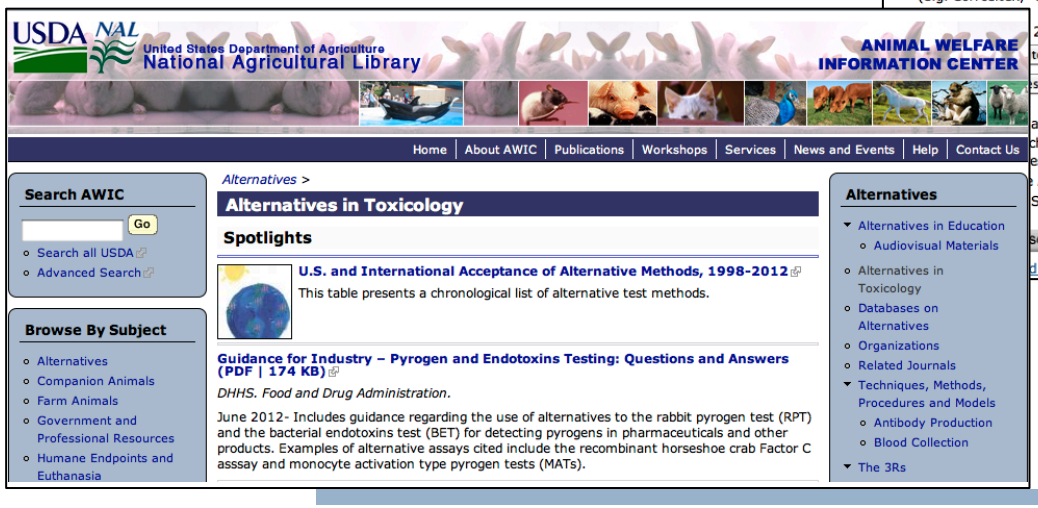
- Why is this important?
  - New and revised methods must be both accepted ***and used*** to impact human health and the 3R's
- How will ICCVAM foster acceptance and use of alternative test methods?
  - Provide guidance on adequate validation study design to ensure data are generated to support regulatory acceptance decisions
  - Carry out high-quality independent scientific peer reviews
  - Provide comprehensive test method evaluations to regulatory agencies and other stakeholders
  - Organize implementation and best practices workshops for stakeholders

Strategic Opportunity:
Promote Regulatory Acceptance and Use of Alternatives

Carry-over Activities Include

- Encourage all 15 member agencies to create and update websites dedicated to alternative test methods.
  - Provide links on the NICEATM-ICCVAM website





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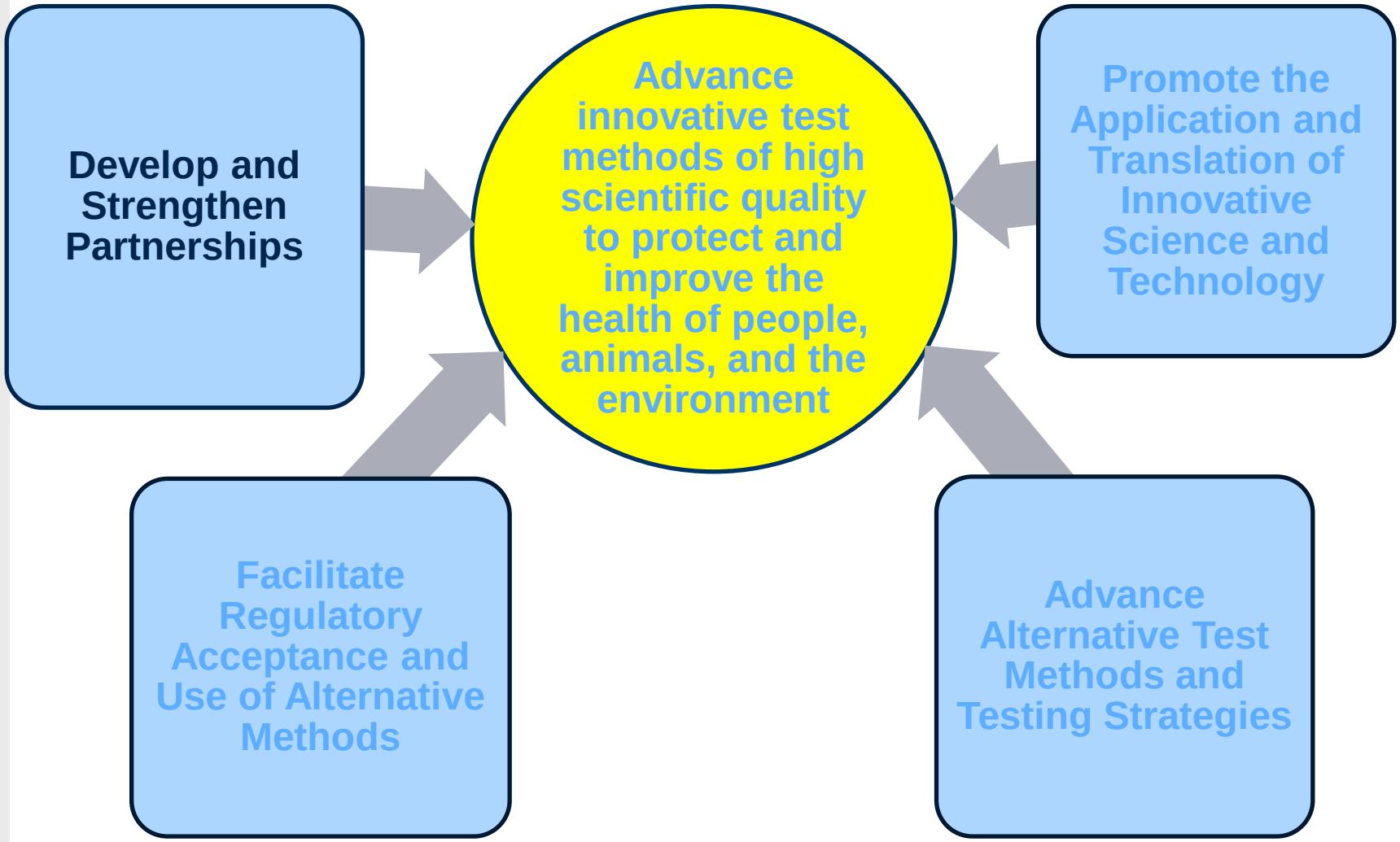
2013-2017 Five-Year Plan:
Key Strategic Opportunity:



Strategic Opportunity: Develop and Strengthen Partnerships

Carry-Over Activities Include

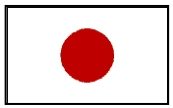
- Promote interagency harmonization of regulatory testing protocols by collaborating with OECD to develop performance standards for international test guidelines
- Co-organize workshops with government and non-governmental organizations that promote alternative methods and ITDS
- Develop international best practices for test method evaluations through collaboration with ICATM partners

Health Canada

NICEATM-ICCVAM

EURL-ECVAM

KoCVAM



JaCVAM

What Do We Plan To Achieve?

- Replace and further reduce animal use wherever scientifically feasible
- Eliminate unrelieved pain and distress where and when animals must still be used
- Continued and improved protection of public health, animal health, and the environment

We look forward to SACATM feedback on priorities and activities as we finalize and implement this Plan!

Acknowledgements

- Five-Year Plan Subcommittee
  - Dr. Joanna Matheson, CPSC, Chair
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  - Dr. Carol Clarke, USDA
  - Dr. Anna Lowit, EPA
  - Dr. Margaret Snyder, NIH
  - Dr. Moiz Mumtaz, ATSDR
  - Dr. Pertti Hakkinen, NLM
  - Dr. Surender Ahir, OSHA
  - Dr. William Stokes, NIEHS
  - Dr. Warren Casey, NIEHS
  - Dr. Rajendra S. Chhabra, NIEHS
  - Ms. Debbie McCarley, NIEHS
  - Dr. Shelia Newton, NIEHS
- ICCVAM
- The 15 ICCVAM Agency Program Offices
- Stakeholders
- Public Commenters
- NICEATM
- NICEATM Support Contractor
- SACATM

Acknowledgements: Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Agency for Toxic Substances and Disease Registry

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Consumer Product Safety Commission

* Joanna Matheson, PhD, **Vice-Chair**
\+ Kristina Hatlelid, PhD

Department of Agriculture

* Jodie Kulpa-Eddy, DVM, **Chair**
\+ Carol Clarke, DVM, DACLAM

Department of Defense

* Patrick Mason, PhD (DRE)
\+ Terry Besch, DVM, DACLAM, DACVPM, (USAMRIID)
\+ Patty Decot (DRE)

Department of Energy

* Michael Kuperberg, PhD

Department of the Interior

* Barnett A. Rattner, PhD

Department of Transportation

\+ Steve Hwang, PhD

* Principal Agency Representative
\+ Alternate Principal Agency Representative

Environmental Protection Agency

Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention

* Anna Lowit, PhD

NHERRL, *Office of Research and Development*

\+ Stepanie Padilla, PhD

National Cancer Institute

* T. Kevin Howcroft, PhD
\+ Chand Khanna, DVM, PhD

National Institute for Occupational Safety and Health

* Paul Nicolaysen, VMD

National Institute of Environmental Health Sciences

* William S. Stokes, DVM, DACLAM
\+ Warren Casey, PhD, DABT
Rajendra S. Chhabra, PhD, DABT
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National Institutes of Health

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What Do We Plan To Achieve?

- Replace and further reduce animal use wherever scientifically feasible
- Eliminate unrelieved pain and distress where and when animals must still be used
- Continued and improved protection of public health, animal health, and the environment

We look forward to SACATM feedback on priorities and activities as we finalize and implement this Plan!