The NICEATM-ICCVAM Five-Year Plan (2008-2012)

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

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PREFACE

The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) prepared this five-year plan in response to requests from the Appropriations Committees of the United States House of Representatives and the U.S. Senate. The plan describes how NICEATM and ICCVAM will foster and promote research, development, translation, and validation of alternative test methods that will reduce, refine, and replace the use of animals for safety testing, while maintaining scientific quality and the protection of human health, animal health, and the environment.

Several Federal agencies are responsible for safeguarding human and animal health and the environment. To assess health and environmental risks, Federal agencies develop and adopt test methods to evaluate the potential hazards or safety of chemicals and other products. Scientists are using advanced science and technology to develop new and revised safety assessment methods that promise to provide improved accuracy, time and cost savings, and further reduction, refinement, and replacement of animal use.

ICCVAM and NICEATM serve a unique role in evaluating the usefulness and limitations of new safety testing methods and helping to achieve acceptance of those found to be scientifically valid for regulatory purposes. This interagency cooperation by 15 Federal agencies and programs provides a more efficient and effective mechanism for Federal test method reviews. ICCVAM seeks to ensure that new and revised test methods meet the needs of Federal agencies while reducing, refining and replacing the use of animals in testing where scientifically feasible. During its first ten years, ICCVAM reviewed and recommended numerous alternative methods that are now accepted and used not only in the U.S. but also throughout our global community. This five-year plan builds on experience gained during those first ten years and describes ICCVAM and NICEATM plans and priorities for the next five years.

ICCVAM and NICEATM are committed to transparency and stakeholder involvement in all activities. Accordingly, this plan was developed with multiple opportunities for public input. As we address the challenges described in this plan, we will seek increased stakeholder collaborations. We are confident that enhanced cooperation will speed the development and validation of alternative test methods of high scientific quality that will further reduce, refine and replace the use of animals in safety testing.

We thank our many government and non-government stakeholders for their continued support of NICEATM and ICCVAM, and look forward to future productive partnerships that will benefit both public health and animal welfare.

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

Marilyn Wind, Ph.D.
U.S. Consumer Product Safety Commission
Chairman, ICCVAM

EXECUTIVE SUMMARY

The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)[1] prepared this five-year plan in conjunction with Federal agency program offices. The plan describes how NICEATM and ICCVAM will facilitate the research, development, translation[2], validation, and regulatory acceptance of alternative test methods that reduce, refine, and replace the use of animals in testing, while maintaining scientific quality and the protection of human health, animal health, and the environment.

The plan addresses ICCVAM's vision (**Appendix A**) to play a leading role in fostering and promoting the development, validation, and regulatory acceptance of scientifically sound alternative test methods both within the Federal government and internationally. Acceptance of such methods will reduce, refine, and replace animal use, while maintaining or improving the protection of human and animal health and the environment.

Implementing this plan involves four key challenges. The first challenge is to identify priority areas for the next five years, and to conduct and facilitate activities in these areas. The second challenge involves identifying and promoting research initiatives that are expected to support the future development of innovative alternative test methods. The third challenge is to foster the acceptance and appropriate use of alternative test methods through outreach and communication. The last challenge is to develop partnerships and to strengthen interactions with ICCVAM stakeholders in order to facilitate meaningful progress.

Identifying Priorities and Conducting and Facilitating Alternative Test Method Activities

ICCVAM priorities emphasize alternatives for those regulatory test methods that can use large numbers of animals and that can involve significant animal pain and distress. Currently, the four highest-priority testing areas are ocular toxicity, dermal toxicity, acute toxicity, and biologics. Other priority testing areas include immunotoxicity, endocrine disruptors, pyrogenicity, reproductive and developmental toxicity, and chronic toxicity and carcinogenicity. Neurotoxicity testing is also an area of interest.

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[1] ICCVAM (The Interagency Coordinating Committee on the Validation of Alternative Methods), a permanent interagency committee administered by NIEHS under NICEATM (the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods), is composed of members designated by the heads of 15 Federal agencies. ICCVAM was created under the ICCVAM Authorization Act of 2000.

[2] ICCVAM considers test method translation activities as those that are carried out to characterize if there is evidence of relevance and applicability of a test method for a specific testing purpose. If so, then the test method may be considered for further evaluation in a formal validation study.

While these represent current priorities and interests, ICCVAM and NICEATM recognize that planning must be flexible in order to take advantage of advances in science and technology and to respond to new testing needs. Integrated testing approaches are emphasized to effectively address the inherent complexity of human and animal responses to toxicants and to maximize the impact of new testing alternatives on reduction, refinement, and replacement of animal use. NICEATM and ICCVAM will continue to facilitate research, development, translation, and validation of alternative test methods by identifying critical knowledge and data gaps for regulatory agencies, the scientific community, and other stakeholders.

Incorporating New Science and Technology

The second challenge is to identify and promote research incorporating new technologies that can be expected to support the future development of new test methods and approaches to reduce or eliminate the need for animals. While many of these approaches will require several years to develop and validate, some may be ready for use more quickly. To maximize the efficiency of this process, NICEATM and ICCVAM are working with Federal agencies and other stakeholders to link research and development activities to the standardization and validation of alternative test methods that may be used in regulatory testing.

Fostering Regulatory Acceptance and Use of Alternative Methods

The third challenge is to foster regulatory acceptance and appropriate use of alternative test methods by promoting active communication and outreach efforts with both government and non-government stakeholders. NICEATM and ICCVAM will provide high quality comprehensive test method background review documents and the results of independent scientific peer reviews to facilitate the approval of these test methods by regulatory agencies and the international community. Once an alternative test method has been accepted, ICCVAM will work to promote the use of the test method by sponsoring and participating in training workshops for interested stakeholders who may generate or review data from the test method.

Developing Partnerships

NICEATM and ICCVAM will further develop partnerships and strengthen interactions with stakeholders while considering advice from their advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). The overall aims of these partnerships are to make the best use of existing resources and scientific expertise, maximize the efficiency of test method validation efforts and evaluations, minimize duplication of effort, and ensure an early exchange of information concerning test method validation. This will facilitate national and international recognition, acceptance, and implementation of scientifically valid alternative test methods.

Monitoring Progress

Regular updates will be provided in the ICCVAM Biennial Progress Report, on the ICCVAM and NICEATM website, and at SACATM meetings.

INTRODUCTION

This document, prepared by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), in partnership with relevant Federal agency program offices, describes a five-year plan to:

- Research, develop, translate[3], and validate new and revised non-animal and other alternative assays for integration of relevant and reliable methods into Federal agency testing programs
- Identify areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the replacement, reduction, and refinement of animal tests, when this is scientifically valid and appropriate

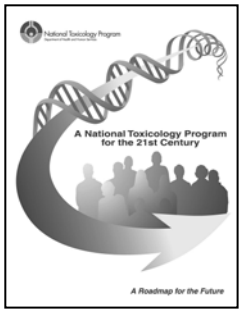
An overall goal is for ICCVAM to assume a greater leadership role in promoting research, development, translation, validation, and regulatory acceptance of alternative test methods. This five-year plan builds on the ICCVAM mission, vision, and strategic priorities (ICCVAM 2004; see **Appendix A**) to help NICEATM and ICCVAM achieve greater progress and to inform the public of their plans and approaches. The plan also builds on the NTP's Roadmap for the 21st Century[4], which includes the goal of developing and validating improved testing methods and, where scientifically feasible, to ensure that these methods reduce, refine, or replace the use of animals. The Roadmap also specifies that activities and assays developed under the NTP Roadmap will be conducted in cooperation and consultation with ICCVAM to maximize their value to regulatory agencies.

Sidebar: Building on the NTP Roadmap for the Future

Goal 2 of the Roadmap: "Develop and validate improved testing methods and, where feasible, ensure that they reduce, refine, or replace the use of animals."

From page 7: "Activities and assays developed under the NTP Roadmap will be done in cooperation and consultation with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to maximize their value to regulatory agencies."

[3] ICCVAM considers test method translation activities as those that are carried out to characterize if there is evidence of relevance and applicability of a test method for a specific testing purpose. If so, then the test method may be considered for further evaluation in a formal validation study.
[4] http://ntp.niehs.nih.gov/files/NTPrdmp.pdf



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Background

U.S. regulatory agencies are charged with protecting human and animal health and the environment (**Appendix B**). As part of this mission, agencies need to determine whether adverse effects might result from exposures to substances such as pesticides, consumer products, medicines, medical devices, workplace chemicals, food additives, or to contaminants in air, food, or water. Many of the current test methods for evaluating hazards and risks from exposure to such substances use laboratory animals. Federal agencies require that all test methods should be based on sound science. According to the ICCVAM Authorization Act of 2000 (see **Appendix E**), new, revised, and alternative test methods must be determined to be valid for their proposed use before agencies can adopt them for regulatory purposes. Validation is required to determine if the use of an alternative test method, compared to current methods or approaches, can provide equal or better protection of human and animal health and the environment.

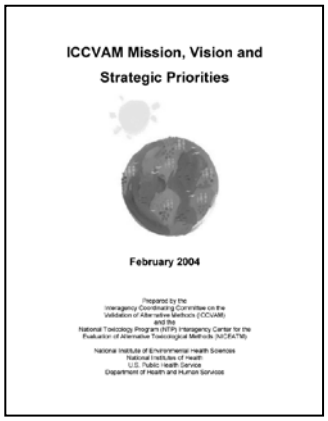
U.S. laws (42 USC 289d, 7 USC 2131 et. seq.) require that alternatives be considered before using animals for research and testing[5]. Such alternatives include new or revised test methods that:

- **Reduce** the number of animals to the minimum required to obtain scientifically valid data
- **Refine** procedures to lessen or eliminate pain and distress to animals
- **Replace** animals with non-animal systems or one animal species with a phylogenetically lower animal species

Reduction, refinement, and replacement alternatives are commonly referred to as "the 3Rs" of alternatives.

[5] This concept is integral to the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*, which are incorporated in the Public Health Service Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/phspol.htm).

Sidebar: The Mission and Strategic Priorities of NICEATM and ICCVAM as outlined in the "ICCVAM Mission, Vision, and Strategic Priorities" (February 2004):



ICCVAM's mission: 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 while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.

Strategic priorities:

- Set priorities for evaluating test methods and carry out the reviews
- Facilitate collaborative scientific validation internationally
- Stimulate development of priority test methods and strategies
- Foster appropriate use of validated test methods
- Strengthen ICCVAM capability and sustainability
- Strengthen interaction with ICCVAM stakeholders

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The Role of ICCVAM and NICEATM

ICCVAM[6] is a permanent interagency committee administered by the National Institute of Environmental Health Sciences (NIEHS) under NICEATM and is composed of members from 15 Federal agencies (**see sidebar**). The mission of

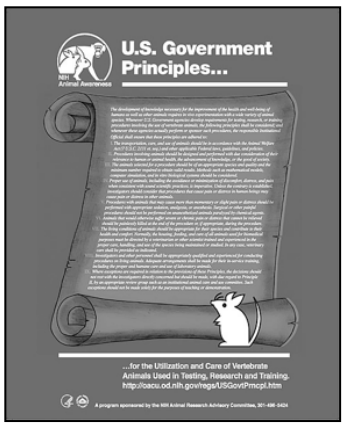
[6] ICCVAM, a Federally mandated interagency committee, provides recommendations to Federal agencies about the scientific validity and usefulness and limitations of proposed test methods. Agencies are required to consider ICCVAM test method recommendations and make decisions on their acceptability. ICCVAM seeks to advance test methods that will ensure the protection of human and animal health and the environment while advancing animal welfare. It does so by facilitating the research, development, translation, and validation activities for alternative methods.

ICCVAM is to facilitate development, validation, and acceptance for regulatory use of new, revised, and alternative test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.

To fulfill this mission, NICEATM and ICCVAM work with a broad range of stakeholders, including Federal agencies, national and international validation and test guideline organizations, industry, academia, and the animal welfare community. Many Federal agencies and other organizations conduct research that could ultimately result in the development and validation of an alternative test method for regulatory use. Thus, ICCVAM depends on its many stakeholders to conduct and achieve successful test method research, development, translation, and validation. These test methods can then be evaluated by ICCVAM for potential regulatory use. These interactions have resulted in the review of 185 test methods by NICEATM and ICCVAM (**Appendix F**). To date, ICCVAM and NICEATM have developed recommendations for ICCVAM member agencies on alternative methods for the four most commonly used toxicity tests.

The following chapters outline the NICEATM-ICCVAM five-year plan by describing the ongoing and planned activities for priority areas directed at reducing, refining, and replacing animal use in regulatory testing. This is followed by a summary of new science and technology being pursued by ICCVAM member agencies as promising approaches to alternative test method development and testing strategies. Finally, the mechanisms for fostering acceptance and appropriate use of alternative test methods and developing partnerships with stakeholders are described.

Sidebar: The U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing Research and Training are the foundation for the 1985 Animal Welfare Act amendment and the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals. Key provisions include:



III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and *in vitro* biological systems should be considered.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain and distress in human beings may cause pain and distress in other animals.

V. Procedures with animals that cause more than momentary pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

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ICCVAM Member Agencies

- Consumer Product Safety Commission (CPSC)
- Department of Agriculture (USDA)

- Department of Defense (DOD)
- Department of Energy (DOE)
- Department of Health and Human Services
  - Centers for Disease Control and Prevention
    - Agency for Toxic Substances and Disease Registry (ATSDR)
    - National Institute for Occupational Safety and Health (NIOSH)
  - Food and Drug Administration (FDA)
  - National Institutes of Health (NIH)
    - Office of the Director
    - National Institute of Environmental Health Sciences (NIEHS)
    - National Cancer Institute (NCI)
    - National Library of Medicine (NLM)
- Department of the Interior (DOI)
- Department of Labor
  - Occupational Safety and Health Administration (OSHA)
- Department of Transportation (DOT)
- Environmental Protection Agency (EPA)

Federal agencies that have statutory authority to conduct research, development, translation, or validation activities

  - Centers for Disease Control and Prevention
    - Agency for Toxic Substances and Disease Registry (http://www.atsdr.cdc.gov)
    - National Institute for Occupational Safety and Health (http://www.cdc.gov/niosh)
- Department of Agriculture (http://www.usda.gov)
- Department of Defense (http://www.dtic.mil/biosys)
- Department of Energy (http://www.doe.gov)
- Department of the Interior (http://www.doi.gov)
- Food and Drug Administration (http://www.fda.gov)
- National Institutes of Health
  - Office of the Director (http://www.nih.gov)
  - National Cancer Institute (http://www.cancer.gov)
  - National Institute of Environmental Health Sciences/National Toxicology Program (http://www.niehs.nih.gov and http://ntp.niehs.nih.gov)

CHAPTER 1
RESEARCH, DEVELOPMENT, TRANSLATION, AND VALIDATION ACTIVITIES FOR PRIORITY TEST METHODS TO REDUCE, REFINE, AND REPLACE ANIMALS IN REGULATORY TESTING

ICCVAM's priorities are based on agency priorities[7] as well as other criteria[8] that include:

- The potential impact that alternative test methods may have on reducing, refining, or replacing the use of animals for testing, taking into consideration the severity of pain and distress and numbers of animals involved
- The potential for the proposed test method(s) to provide improved prediction of adverse health or environmental effects
- The applicability of testing alternatives across agencies

ICCVAM uses these criteria to prioritize test method nominations and submissions for evaluation.

Priority Activities

This chapter describes ICCVAM's priority areas based on these criteria. Currently, the four highest priorities are ocular toxicity, dermal toxicity, acute toxicity, and biologics. Other priority areas include immunotoxicity, endocrine disruption, pyrogen testing, reproductive/developmental toxicity, and chronic toxicity/carcinogenicity. These priorities will likely evolve over time in response to new testing needs and advances in science and technology.

The inherent complexity of human and animal responses to toxicants means that it is unlikely that any single alternative test method will be able to serve all regulatory needs for a specific testing area. Rather, integrated approaches using batteries of two or more alternative test methods combined with other information about the properties of a test substance will likely be needed to significantly reduce or replace the use of animals for each type of testing. As outlined below, these integrated approaches are being investigated for a number of different toxicity testing areas. Such approaches may be critical to the development of successful hazard assessment methodologies for complex endpoints such as carcinogenicity or reproductive/developmental toxicity, which can result from effects on many different pathways. A priority for each of the areas identified below is the collection and use of available human, animal, and ecological data to assess the performance of existing and new test methods for protecting human and animal health and the environment.

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[7] Testing priorities of individual Federal agencies may differ because of the different statutory mandates under which they operate (**Appendix B**).

[8] http://iccvam.niehs.nih.gov/SuppDocs/submission.htm

Ocular Toxicity Testing

The evaluation of alternative methods for ocular (eye) safety testing is one of ICCVAM's four highest priorities because it is required by multiple agencies as one of the four most commonly required product safety tests and can therefore involve large numbers of animals, and because rabbits used in tests to identify ocular hazards can experience significant pain and distress when eye injuries occur. Regulatory agencies require identification of potential ocular hazards to warn consumers and workers when exposure to a chemical or product may cause blinding or other kinds of eye damage. Two critically important goals are the replacement of the rabbit eye test with one or more alternative assay(s) that can provide equal or greater prediction of these types of hazards, and the implementation of procedures to avoid pain and distress where animals must still be used. NICEATM and ICCVAM recently evaluated and recommended two *in vitro* test methods that can be used to identify certain types of substances that cause permanent and severe eye damage and that do not use animals[9]. *NICEATM and ICCVAM will carry out activities to improve the usefulness and applicability of these test methods. In addition, in collaboration with the European Centre for the Validation of Alternative Methods (ECVAM), NICEATM and ICCVAM will evaluate the use of these and other in vitro test methods for accurately identifying substances that cause reversible eye damage or that do not damage the eye. NICEATM and ICCVAM will also evaluate in vitro approaches for determining the ocular irritation potential of antimicrobial cleaning product formulations, and will facilitate the submission of in vivo reference data to be added to a database for use in expanding the development and applicability of new alternative ocular test methods.*

NICEATM and ICCVAM recently organized scientific symposia[10] on "*Mechanisms of Chemically-Induced Ocular Injury and Recovery,*" and "*Minimizing Pain and Distress in Ocular Toxicity Testing.*" Symposia recommendations for relevant research, development, and validation studies have been provided to the scientific and regulatory communities for consideration. *NICEATM and ICCVAM will encourage stakeholders to carry out the recommended studies, and will evaluate new methods or combinations of in vitro test methods that are developed to reduce or replace animal use for corrosivity and irritation testing. In addition, a comprehensive review of the use of topical anesthetics and systemic analgesics for reducing pain and distress will be conducted to determine their applicability in ocular testing.*

[9] http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox.htm
[10] http://iccvam.niehs.nih.gov/meetings/ocumeet/sympinfo.htm

Biologics Testing

Biological products (commonly referred to as biologics) include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, monoclonal antibodies, and recombinant therapeutic proteins that are used to treat or protect humans or animals. Biologics testing is also one of ICCVAM's four highest priorities because it can require large numbers of animals that may experience significant pain and distress during testing, and it is required by multiple agencies. As such, it is important to identify *in vitro* alternatives to the current *in vivo* tests that provide equal or greater protection of human or animal health, and to identify procedures that can be used to reduce or avoid pain and distress where animals must still be used. Alternative test methods are under development that target reduction and replacement of animal testing with *in vitro* test methods, as well as refinement of animal testing through modifications to the current animal tests. To facilitate the development of these types of alternatives, ICCVAM, NICEATM, and ECVAM recently co-sponsored a workshop that identified activities needed to further reduce, refine, and replace the use of mice for determining the effectiveness of a biologic product[11]. *NICEATM and ICCVAM will evaluate alternative test methods and testing strategies for vaccine potency testing and will facilitate the acceptance of adequately validated test methods and humane endpoints found to be sufficiently accurate and reliable. A priority for evaluation will be an in vitro vaccine potency test being developed by the USDA to reduce the numbers of animals required to evaluate the potency of a common veterinary bacterial vaccine for Leptospirosis*.

Dermal Toxicity Testing

The evaluation and development of alternatives for dermal (skin) safety testing is also one of ICCVAM's four highest priorities because it is required by multiple agencies as one of the four most commonly required product safety tests and therefore can involve large numbers of animals, and because rabbits used in tests to identify dermal hazards can experience significant pain and distress. Regulatory agencies require identification of dermal hazards to warn consumers and workers when exposure to a chemical or product may cause skin corrosivity (permanent scarring/burns) or irritation. This information is used to determine appropriate precautions needed to avoid such injury. Test results are also used to determine appropriate packaging to minimize dangerous spills during transport. ICCVAM's ultimate goal in this area is the replacement of the rabbit skin test for both corrosivity and irritation with alternative methods that meet the requirements of U.S. regulators.

[11] http://iccvam.niehs.nih.gov/methods/biologics/biologics.htm

In vitro alternatives for dermal corrosivity have been developed, and several of these test methods have been recommended and accepted for regulatory use as screening methods[12]. In appropriate circumstances, substances yielding positive results can be classified and labeled as corrosives without the use of animals. *NICEATM and ICCVAM will evaluate alternative dermal irritation test methods for their usefulness and limitations in U.S. regulatory testing. This will include an evaluation of the use of a combination of in vitro test methods for both corrosivity and irritation to reduce or replace animals. NICEATM and ICCVAM will also evaluate non-animal methods and approaches for determining the skin irritation potential of antimicrobial cleaning products.*

Sidebar: Working Towards Replacement

ICCVAM has organized independent scientific peer reviews of the usefulness and limitations of *in vitro* corrosivity test methods for use as alternatives to the *in vivo* rabbit skin and eye tests. By using these alternative methods, animal testing of substances can be avoided that would otherwise cause corrosive injuries to the skin or eyes of rabbits.

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Acute Toxicity Testing

Acute toxicity testing is the most commonly conducted product safety test worldwide. It is also one of ICCVAM's four highest priorities because it is required by multiple agencies and therefore can involve large numbers of animals, and because it can result in significant pain and distress to test animals. Until the recent adoption of alternative rodent tests that use significantly fewer animals and international guidance on humane endpoints, a rodent acute oral test using a large number of animals with death as an endpoint was used to satisfy the requirements of agencies to appropriately label products that cause acute toxicity (poisoning). ICCVAM has contributed significantly to recent progress in reducing and refining acute toxicity testing, For example, ICCVAM evaluated and recommended an alternative animal test method[13] that has now been accepted by regulatory agencies as a replacement for the traditional acute oral toxicity test. This alternative test method can reduce the use of animals for this purpose by up to 70%. NICEATM and ICCVAM were also involved in the development of international guidance for humane endpoints that can be used as criteria to euthanize animals rather than allowing them to die during the study. The ultimate goal is to find ways to conduct acute oral toxicity testing without animals. In support of this goal, ICCVAM evaluated and recommended two cell culture test

[12] http://iccvam.niehs.nih.gov/methods/dermal/corrode.htm
[13] http://iccvam.niehs.nih.gov/methods/acutetox/udp.htm

methods that, while not sufficiently accurate to replace animals, can be used to estimate the starting doses for animal studies[14], and thereby further reduce the number of animals needed for each test.

An independent peer review panel made several recommendations to ICCVAM for future studies to advance the use of *in vitro* methods for assessing acute oral toxicity. In response to these recommendations, ICCVAM plans to carry out several related activities to promote further development of non-animal replacements, to expand the use of the *in vitro* test methods to further reduce animal use, and to further reduce the potential pain and distress associated with acute toxicity testing. *NICEATM and ICCVAM will organize an international workshop to (1) identify standardized procedures for collecting mechanistic information from acute oral toxicity testing to aid in developing batteries of predictive in vitro test methods that can further reduce and eventually replace animals for acute toxicity testing, and (2) seek more predictive and more humane endpoints that may be used to terminate studies earlier in order to further reduce pain and distress. In addition, NICEATM will conduct a study to determine how the two cell culture test methods can be used to set the starting dose for mixtures, which represent a significant percentage of acute testing studies. NICEATM will also assemble high quality rodent acute oral toxicity data (either from previous studies or, in cooperation with industry, from future required regulatory studies) and make this reference database available for the development and validation of other new in vitro tests (or batteries of tests) to more accurately predict oral acute systemic toxicity. NICEATM and ICCVAM will look for opportunities to collaborate with the ECVAM ACuteTox Project[15], which seeks to develop an in vitro testing strategy to predict human acute oral toxicity in order to replace the animal acute oral toxicity tests currently used for regulatory purposes. This could include evaluating the state of science to better understand the key pathways involved in acute oral toxicity. NICEATM and ICCVAM will also consider potential alternative methods for acute dermal systemic toxicity and acute inhalation toxicity.*

Sidebar: Reduction Alternative: An ICCVAM Success Story

In 2002, ICCVAM recommended the revised Up-and-Down Procedure (UDP) as a replacement for the conventional acute oral systemic toxicity test. The UDP can reduce the use of animals for this type of testing by up to 70%. All Federal regulatory agencies that require acute oral toxicity testing have accepted the revised UDP. In 2007, ICCVAM recommended that, prior to testing in animals, in vitro cytotoxicity test methods should be considered as one way to estimate the

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[14] http://iccvam.niehs.nih.gov/methods/acutetox/acutetox.htm
[15] http://www.acutetox.org/

starting dose for the revised UDP. This approach is expected to further reduce the number of animals required for an acute toxicity test by up to 20%.

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The ATSDR, DOI, EPA, FDA, and NIH also have ongoing or planned activities relevant to the 3Rs for testing chemicals for acute toxicity. These activities include consideration of modifications to current animal tests to reduce the number of animals used where possible, as well as evaluations of *in vitro* test methods to be used independently or in combination with other tests as possible replacements for animal tests. *NICEATM and ICCVAM will work with these agencies to assist in characterizing the usefulness and limitations of these methods and to foster their appropriate use among the regulated community*.

Immunotoxicity Testing

Immunotoxicity testing is an ICCVAM priority because it can result in significant pain and distress to test animals, can involve large numbers of animals, and is required by multiple Federal agencies. Regulators use skin sensitization tests to identify substances that might cause this response in humans following repeated skin exposure. The Murine Local Lymph Node Assay (LLNA) is an alternative test method used for skin sensitization testing that reduces the number of animals needed, reduces the time required for testing, and can substantially reduce or minimize the pain and distress associated with the traditional testing method. The LLNA was the first alternative test method evaluated and recommended by ICCVAM, and it has been accepted by regulatory agencies[16]. Based on this evaluation ICCVAM prepared a test guideline for the LLNA that has been accepted by the Organisation for Economic Co-operation and Development (OECD). *NICEATM and ICCVAM will evaluate whether or not the LLNA can be used as a stand-alone method for the determination of potency (including severity) and evaluate the possible expansion of the scope of substances and mixtures for which the LLNA may be used. NICEATM and ICCVAM will also evaluate a number of modifications to the LLNA that may further reduce the number of animals used, or that may eliminate the need to use radioactive materials as part of the protocol*[17].

Additional assays are under development that may reduce, refine, or replace the use of animals in skin and respiratory sensitization testing. *Where appropriate, NICEATM and ICCVAM will review and foster approaches to incorporate valid computational and in vitro methods into laboratory testing strategies*. This will

[16] http://iccvam.niehs.nih.gov/docs/immunotox_docs/llna/llnarep.pdf
[17] http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm

include closely following the ECVAM Sens-It-IV Project[18] that seeks to develop *in vitro* alternatives for identifying potential skin or lung sensitizers.

Sidebar: Refinement Alternative: Minimizing Pain and Distress

ICCVAM recommended the Murine Local Lymph Node Assay (LLNA) as a valid substitute for the guinea pig maximization test in many testing situations. The LLNA can substantially reduce or minimize the pain and distress in treated animals that can result from sensitizing chemicals, and also requires fewer animals. Based on the recommendations of ICCVAM and an independent scientific peer review panel, the LLNA is accepted as an alternative to the guinea pig test for assessing allergic contact dermatitis by U.S. regulatory agencies. Following an implementation workshop co-sponsored by ICCVAM and the International Life Sciences Institute (ILSI), the LLNA was incorporated into an international test guideline by the thirty member countries of the Organisation for Economic Co-operation and Development (OECD). ICCVAM is now evaluating the validation status of modifications to the LLNA that may further reduce the number of animals used, expand the usefulness of the LLNA, and eliminate the need to use radioactive materials. ICCVAM is also evaluating the usefulness of the LLNA for assessments of sensitization potency (strength of response). Successful validation in these areas could broaden the use of the LLNA and thus significantly increase the impact of the LLNA as a refinement alternative.

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Endocrine Disruptor Testing

Endocrine disruptor testing is an ICCVAM priority because some types of testing can involve large numbers of animals, may involve significant pain and distress, and may be of use to multiple agencies. A variety of substances have been shown to affect hormones or processes involving hormones, sometimes resulting in developmental or reproductive problems for humans or other species; these substances are called endocrine disruptors. Laws passed in 1996 mandate the development and implementation of a screening program for endocrine disruptors. Programs are being developed throughout the world, including the United States, to screen for chemicals that might interfere with the endocrine systems of humans or wildlife. These programs could result in the use of large numbers of animals if valid alternatives to the current animal tests are not identified. NICEATM and ICCVAM recently reviewed a number of *in vitro* tests designed to detect chemicals that might act as, or interfere with, male and/or female hormones[19]. Based on this review, ICCVAM provided recommendations for future test method

[18] http://www.sens-it-iv.eu/
[19] http://iccvam.niehs.nih.gov/methods/endocrine/end_bckgnd.htm

development and validation activities that are being implemented in studies by the EPA and NICEATM[20]. Related test methods for detecting chemicals that might act like or inhibit estrogen have recently been nominated for evaluation[21]. *NICEATM will lead a joint international study with ECVAM and the Japanese Center for the Validation of Alternative Methods (JaCVAM) to evaluate the usefulness and limitations of an in vitro test method to identify estrogen-like chemicals that does not require the use of animals as donors for test components.*

NICEATM and ICCVAM, working primarily through the U.S. National Coordinator for the OECD Test Guidelines Program, are also increasing their involvement in OECD test guideline activities related to endocrine disruptors. This includes an early exchange of information concerning test method validation. It also includes working together with international stakeholders, where possible, to best utilize existing resources to maximize the efficiency of evaluation/validation efforts towards the goal of facilitating national and international recognition, acceptance, and implementation of scientifically valid test methods.

Pyrogen Testing

Products injected or implanted into the body must be appropriately shown to be free of pyrogens (substances that could cause fever) and other adverse health effects prior to their use in humans and animals. Although these types of pyrogen tests are of primary concern to several programs in one agency (that is, the FDA), they can require large numbers of animals that might experience pain and distress. Therefore, pyrogen testing is considered an ICCVAM priority. Recently, alternative pyrogenicity test methods based on the activation of cultured human blood cells have been developed that take advantage of the role of these cells in the fever response. ICCVAM recently evaluated five such *in vitro* test methods proposed as potential replacements for the current rabbit test[22]. *ICCVAM will issue recommendations on the current usefulness of these test methods and recommendations for future studies that may support their expanded use. Once additional studies have been completed, ICCVAM will re-evaluate the validation status of these test methods*.

Reproductive and Developmental Toxicity Testing

Reproductive and developmental toxicity testing is an ICCVAM priority because it is required by multiple agencies, uses large numbers of animals, and can involve pain and distress to test animals. ICCVAM evaluated the usefulness and limitations of the Frog Embryo Teratogenesis Assay - *Xenopus* (FETAX) to

[20] http://iccvam.niehs.nih.gov/docs/endo_docs/edfinalrpt0503/edfinrpt.pdf
[21] http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm
[22] http://iccvam.niehs.nih.gov/methods/pyrogen/pyrogen.htm

measure the effects of chemicals on mortality, malformation, and growth inhibition[23]. This assay was proposed as a screen to identify potential developmental toxicants. Although FETAX was not considered sufficiently reproducible for regulatory use, ICCVAM endorsed the recommendations of an independent expert peer review panel that further studies should be conducted to improve test method performance. In addition, the panel and ICCVAM recommended a list of reference substances that can be used for validation studies of this and other developmental toxicity methods.

Renewed emphasis will be placed on identifying mechanism-based tests that could be useful in understanding one or more of the many different pathways involved in reproductive or developmental toxicity. For example, the FDA is involved in development of *in vitro* tests that could reduce the number of animals used in developmental toxicity testing. However, the complexity of these endpoints means that it is unlikely that any single alternative test method will be able to serve all regulatory needs. *NICEATM and ICCVAM will closely follow the ECVAM ReProTect project[24], a consortium of European partners working towards the development of in vitro testing batteries that will provide detailed information on the hazards of compounds to the reproductive cycle. ICCVAM will also explore, and promote, where appropriate, possible revisions to existing in vivo testing protocols to reduce the overall number of animals required without compromising assay performance.*

Chronic Toxicity/Carcinogenicity Testing

Chronic toxicity and carcinogenicity testing is an ICCVAM priority because these methods are required by multiple agencies, use large numbers of animals, and may involve significant pain and distress from resulting systemic effects and cancers. Two-year studies approximating lifetime exposure in rats and mice remain the primary method by which chemicals are tested for their potential to cause cancer and chronic disease in humans. NIEHS and FDA are involved in the research and development of alternative models that could reduce the number of animals used and shorten the duration of these tests. The development and validation of the battery of alternative test methods needed to serve all regulatory needs in this area will likely take longer than the five-year time frame for this strategic plan. *However, ICCVAM and NICEATM will facilitate efforts towards developing alternative models for one or more of the multiple mechanisms associated with these endpoints, and that better simulate living organisms.*

Federal regulatory agencies also typically require the use of tests that evaluate genetic toxicity, the ability of chemical or physical agents to damage the DNA

[23] http://iccvam.niehs.nih.gov/methods/development/dev.htm
[24] http://www.reprotect.eu/

and/or chromosomes of cells. Genetic toxicity can potentially contribute to the cancer-causing or developmental toxicity potential of a chemical. Although genetic toxicity testing is not currently considered a substitute for carcinogenicity testing, the FDA is studying the usefulness and limitations of various human primary cells and cell lines for use in genetic toxicity testing. *NICEATM and ICCVAM are participating in a JaCVAM-sponsored international validation study (which also includes ECVAM) of an alternative animal test (that is, the alkaline Comet assay) to determine the induction of DNA damage in cells of multiple organs. If the JaCVAM validation study is successful, there are plans for the possible validation of an in vitro Comet assay that might be incorporated into the battery of genetic toxicity assays.*

Other Toxicity Areas of Interest

NICEATM and ICCVAM recognize that there are other areas of toxicity testing for which alternative test methods are needed. Identifying alternative test methods for potential neurotoxins (chemicals that affect the nervous system) is a priority of the FDA and the NIH. Both agencies are involved in the development of *in vitro* methods to identify biomarkers of neurotoxicity. *NICEATM and ICCVAM will closely follow ongoing efforts in these areas and will work to identify the most useful tests and to facilitate their review and acceptance.*

CHAPTER 2
INCORPORATING NEW SCIENCE AND TECHNOLOGY

NICEATM and ICCVAM will identify and promote research incorporating new technologies that can be expected to support the future development of new test methods and approaches to reduce and eliminate the need for animals. While many of these approaches will require several years of development and validation, some may be ready for use more quickly. To maximize the efficiency of this process, NICEATM and ICCVAM are working with Federal agencies and other stakeholders to link research and development activities to the standardization and validation of alternative test methods that may be used in regulatory testing.

High Throughput Screening

The NTP promotes improvements in toxicology test methods that will enhance its ability to efficiently evaluate large numbers of substances in the environment for which there is little or no information about potential adverse effects. In this regard, NTP is working to identify or develop rapid biochemical or cell-based tests that can be used to screen large numbers of environmental substances for their potential biological activity (that is, high throughput screening [HTS]). The results of HTS experiments provide a starting point for understanding the potential human and animal toxicity of the substances to be tested, and might be useful in setting priorities for more comprehensive testing. The NTP HTS activities are coordinated with similar activities being conducted by the EPA and organizations such as ECVAM. One goal of these studies is to identify batteries of HTS assays that ultimately may reduce or replace the use of animals in toxicological tests. *This approach follows the National Research Council's recently published vision and strategy of toxicity testing in the 21st century, which emphasizes the development of predictive high throughput assays to evaluate alterations to key toxicity pathways*[25]*. Furthermore, such activities and assays that are developed under the NTP Roadmap will be conducted in cooperation and consultation with ICCVAM to maximize their value to regulatory agencies. In this regard, NICEATM and ICCVAM will facilitate reviews of the usefulness and limitations of defined HTS approaches, and also assist in the identification of assays and endpoints that are relevant for alternative test methods that have already been adopted.*

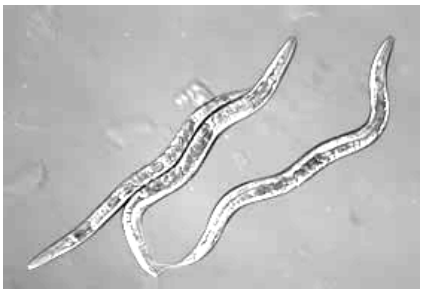
Other Animal Systems

Both the NIEHS and the FDA are evaluating the roundworm (*Caenorhabditis elegans)* for its usefulness as a more rapid method to provide information about

[25] http://books.nap.edu/catalog/11970.html

potential adverse human health effects of chemicals[26]. A short life cycle, easy and inexpensive maintenance and culturing, and detailed knowledge of its biology has allowed for the development of rapid low-cost assays that provide information potentially relevant to various types of toxicity. Because many of the *C. elegans* genes are the same as those of more complex animals (including humans), it is possible that many of the responses elicited in *C. elegans* can be related to other species. *NICEATM and ICCVAM will evaluate the validation status of future tests with this model system that have utility for regulatory testing*.

Sidebar



The roundworm C. elegans is being evaluated as an alternative species for toxicity testing. Because the genes involved in many biological processes (for example, the stress response) have remained essentially unchanged throughout evolution, responses elicited in C. elegans may be applicable to understanding similar processes in higher organisms, including humans. Testing using this organism can be adapted to automated laboratory systems, which allow for increased throughput.

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Through the U.S. National Coordinator for the OECD Test Guidelines Program, EPA is working in concert with OECD member countries to develop assays to evaluate various toxicity endpoints in fish and amphibians. This includes a multi-phased project to validate and peer review an amphibian metamorphosis (tadpole) assay, which will help to assess the potential of chemicals to interact with the thyroid system. This work will help assess the utility of these tests for predicting mammalian and non-mammalian effects. *NICEATM and ICCVAM will closely follow these efforts, and if considered appropriate, will facilitate evaluation of the validation status of these types of test methods.*

[26] see http://www.nih.gov/science/models/ and http://dir.niehs.nih.gov/dirlt/genomics.htm

Computational Approaches

Using data generated from a collection of high throughput bioassays that measure interactions with proteins or genes (e.g. microarrays[27]), EPA is developing computer models for prioritizing chemicals for toxicology testing. This will result in a "toolbox" (referred to as ToxCast™) that will be used for prioritizing chemicals for toxicology evaluation. If the preliminary phases are successful, the EPA will proceed to an implementation phase where profiles of chemicals in need of toxicological evaluation will be obtained and used to develop recommendations for testing priorities.

ATSDR is also developing and applying computational methods to prioritize testing of chemicals of concern and to direct targeted research. Through these activities, ATSDR provides guidance for efficient experimental design, including the determination of appropriate doses for testing chemicals and mixtures.

The DOE is developing computer models for studying the biological effects of radiation. These models will help estimate the minimum number of animals that are needed in experiments dealing with low-dose radiation exposure. They may also help make decisions regarding the possible use of *in vitro* models instead of live animals.

Biomarkers of Toxicity

The NIEHS and the FDA are evaluating biomarkers that could be used in current toxicology tests to predict damage to a specific organ. Such biomarkers may be used as the basis for early humane euthanasia to reduce or relieve the pain and distress experienced by animals with tumors or chronic disease. They will also support the development of predictive *in vitro* screening tests. ATSDR and the National Center for Environmental Health, in collaboration with NIEHS, EPA, NCI, the Armed Forces Institute of Pathology, and the International Commission for Occupational Health, recently organized an international conference on *Biomarkers for Toxicology and Molecular Epidemiology* (Fowler et al., 2005). This conference evaluated advances in biomonitoring technologies and the translation of biomarker endpoints for human epidemiological studies to a number of adverse health outcomes including target organ system toxicity and cancer.

NTP subsequently organized a workshop on *Biomarkers for Toxicology Studies*[28] to identify biomarkers related to injury or altered function of heart, lung, and lipid/carbohydrate metabolism. These biomarkers could be included in toxicology tests to better understand the development of environmentally induced diseases. As a result, the NTP has begun including serum cholesterol and triglycerides to

[27] http://dir.niehs.nih.gov/microarray/
[28] http://ntp.niehs.nih.gov/index.cfm?objectid=B743FF81-F1F6-975E-7E71E3A844E0612E

their clinical pathology panel as routine measures in toxicity tests. Assays for several other biomarkers are undergoing standardization and validation. The NIEHS and the FDA are also exploring gene chip technologies that may allow for the identification of sets of biomarkers that are more predictive of risks or benefits than a single biomarker. *NICEATM and ICCVAM will follow the progress in these areas.*

Toxicology Databases

NIEHS is developing searchable databases of toxicological information that will be made available to the general public via the Internet. These databases will be a source of high quality animal test data that can be used as reference data for comparison to new non-animal test methods. For example, NICEATM will be making a database available that contains rabbit eye test data from ocular toxicity studies. The database will provide the user with detailed protocol information, test substance information, and animal response information. *As part of the NICEATM and ICCVAM priority to encourage the development of new test methods, this database will also incorporate other types of toxicity data that can be used for the development/validation of other types of non-animal test methods (for example, dermal toxicity, in vitro cytotoxicity).*

The Chemical Effects in Biological Systems (CEBS) Knowledgebase[29] is being developed by NIEHS to promote a systems biology approach to understanding the biological effects of environmental stressors. CEBS will house data derived from studies on the effects of environmental chemicals on genes, proteins, and metabolism. Specifics for each study, including study design details, treatment protocols, animal characteristics and toxic endpoints, will be available. All of these data types can be integrated to enable data query and analysis in a biologically meaningful manner. CEBS contains data from both *in vivo* and *in vitro* studies, primarily in rodents, but can house data from other species (for example, humans). This integration of data should improve the understanding of how *in vitro* endpoints could be used to predict *in vivo* effects, and aid in overcoming a critical barrier to the replacement of animals in testing. *NICEATM and ICCVAM will promote the availability of data from CEBS for use in the development of alternative test methods.*

Emerging Needs: Nanomaterials Testing

Nanotechnology is the control of matter at dimensions of roughly 1 to 100 nanometers (a nanometer is one-billionth of a meter; a sheet of paper is about 100,000 nanometers thick), and is being applied in many fields in the physical and biological sciences to create improved materials, devices, and systems. The

[29] http://cebs.niehs.nih.gov/

unique characteristics of nanomaterials can affect their toxicity. Because hazards associated with these types of materials have yet to be characterized, the applicability of current toxicity tests to nanomaterials will have to be evaluated, and new tests may be needed for regulatory use. The number of tests needed to characterize potential hazards of nanomaterials could be very large, as could the number of animals required for such testing. *NICEATM and ICCVAM will work with regulators and stakeholders to identify tests that might be useful, while also addressing the 3Rs.*

CHAPTER 3
FOSTERING ACCEPTANCE AND APPROPRIATE USE OF ALTERNATIVE TEST METHODS

NICEATM and ICCVAM will promote active communication and outreach efforts with both government and non-government stakeholders. These efforts are aimed at encouraging the use of scientific approaches to validation that will generate the information and data that Federal agencies need in order to accept scientifically valid new and revised alternative test methods[30]. While NICEATM and ICCVAM promote and employ good science in determining the validation status of alternative test methods, only Federal agencies can accept these test methods and determine how they might be used in their respective programs. The extent of acceptance by Federal agencies will depend on several factors, including their legislative mandate(s) and policies that are in place to carry out these mandates. *Once regulatory authorities have accepted an alternative test method, ICCVAM will work to promote its use.*

N*ICEATM and ICCVAM will foster the use of alternative test methods by broadly communicating the outcomes of ICCVAM review activities and/or workshops via the Federal Register, at national or international scientific meetings, via peer reviewed journal publications, and at training courses. Emphasis will also be placed on making the scientific community, including Institutional Animal Care and Use Committees (IACUCs), aware of new alternatives that are available for consideration in complying with the PHS policy[31] and Animal Welfare Act provisions, which state that such methods be considered prior to testing in animals, where applicable. The NICEATM and ICCVAM website provides information related to new test methods and past, current, and future activities of NICEATM and ICCVAM. The website will continue to provide user-friendly access to the latest information on validation processes and the most up-to-date*

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[30] ICCVAM provides criteria for adequate validation and regulatory acceptance of test methods for its many stakeholders. These criteria and the process for achieving regulatory acceptance of scientifically valid test methods are described in the report, *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the Ad Hoc Interagency Coordinating Committee on the Validation of Alternative Methods* (http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf). Validation involves determining the usefulness and limitation of a test method for a specific purpose. This includes determining the extent to which a test method will produce similar results in different laboratories around the world, and determining the extent that the test method can correctly measure or predict the biological effect of interest. ICCVAM welcomes nominations or submissions of proposed alternative or revised test methods. To aid test developers with this process, ICCVAM has published guidance on the information and data that is needed to support test method nominations and submissions in the report, *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods* (http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.htm

[31] http://grants.nih.gov/grants/olaw/references/phspol.htm

status of the alternative test methods previously reviewed and those currently under review. One or more lists of frequently asked questions (FAQs) will be developed to provide quick reference guides to broad issues related to the ICCVAM test method evaluation process, as well as more specific issues relevant to individual toxicity testing areas. NICEATM and ICCVAM will use a combination of e-mail and website announcements to inform the public of the availability of newly published Federal Register notices, NICEATM documents, journal articles, and upcoming events. Additionally, ICCVAM and NICEATM will encourage member agencies to create websites dedicated to their specific activities associated with alternative test methods research, development, translation, and validation. NICEATM and ICCVAM will in turn provide a link on their website to these member agency websites.

Sidebar: Partnering with Stakeholders

ICCVAM co-sponsors implementation workshops to encourage interested stakeholders to use valid alternative test methods. For example, in partnership with the EPA and the International Life Sciences Institute, ICCVAM convened a training workshop on acute toxicity testing methods (http://www.ilsi.org/file/ACF220.pdf). The workshop provided practical information and case studies to facilitate the understanding and implementation of the UDP and other *in vivo* and *in vitro* alternative methods for acute toxicity. In addition, because calculation of dose levels to be used in the UDP test method requires complex algorithms, workshop participants were provided free software and training on its use.

(end sidebar text)

ICCVAM will sponsor and participate in workshops that include both government and non-government stakeholders to increase the acceptance and use of new alternative test methods. ICCVAM and NICEATM will actively seek international participation in workshops as well as international scientific partnerships on validation study designs and test method evaluations, such as those described in Chapter 4. This will help ensure that studies conducted with proposed alternative test methods will facilitate international acceptance of alternative test methods. This international participation should also streamline the validation process and avoid unnecessary duplication of effort.

NICEATM and ICCVAM will facilitate the international adoption of valid alternative test methods by providing standardized protocols that can be considered for adoption by international organizations (for example, the International Standards Organization [ISO], OECD, etc.). As appropriate, NICEATM and ICCVAM will provide comprehensive test method background

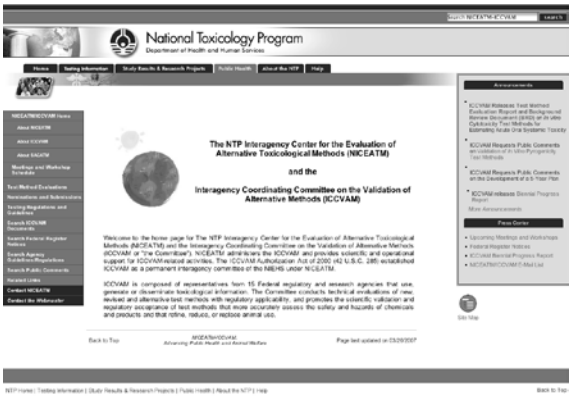
review documents and the results of independent scientific peer reviews to facilitate the approval of these test methods by the international community.

Sidebar

The NICEATM-ICCVAM website contains background information on NICEATM and ICCVAM, current information on ICCVAM test method evaluation activities, guidance on preparing nominations and submissions to ICCVAM, details on upcoming events, and links to other sites of interest. It currently features four searchable databases:

- NICEATM and ICCVAM publications
- Federal and international regulatory documents
- Federal Register notices relevant to NICEATM and ICCVAM activities
- Public comments on NICEATM and ICCVAM activities

Please visit the website at iccvam.niehs.nih.gov.



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CHAPTER 4
DEVELOPING PARTNERSHIPS AND STRENGTHENING INTERACTIONS WITH ICCVAM STAKEHOLDERS

A critical aspect of this plan is the development of partnerships and the strengthening of interactions with ICCVAM stakeholders to promote research, development, translation, and validation activities for alternative test methods. NICEATM and ICCVAM recognize that effective interaction with stakeholders is an essential component of successfully protecting human and animal health and the environment while implementing the 3Rs. Progress and success in the activities outlined in this plan depend on the collective resources, efforts, and scientific breakthroughs of many different national and international stakeholder organizations (for example, government, industry, animal welfare). To facilitate the advancement of alternatives for making regulatory decisions, NICEATM and ICCVAM will identify needs and encourage activities for areas of high priority, taking into consideration the advice of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a Federally chartered advisory committee for NICEATM and ICCVAM.

ICCVAM welcomes nominations or submissions of proposed alternative or revised test methods. To aid test developers with this process, ICCVAM has published guidance on the information and data that is needed to support test method nominations and submissions[32], as well as criteria for validation and regulatory acceptance[33]. NICEATM and ICCVAM also recognize that they must assume a greater leadership role by identifying needs for alternative test methods and encouraging activities for those considered high priority. In this regard, NICEATM and ICCVAM, along with its working groups, will be more proactive in identifying research needs and promising methods that should be priorities for further development, translation, validation, or ICCVAM evaluation.

NICEATM and ICCVAM will foster interagency collaboration among Federal research and regulatory agencies, including opportunities for test method validation activities. This also includes promoting interagency harmonization of regulatory testing protocols, where appropriate, that encourage reduction, refinement, or replacement of animal test methods. Similarly, the continued involvement of representatives from multiple centers within large agencies fosters intra-agency collaboration. Areas of mutual interest might include evaluating, where appropriate, the performance of current test methods for protecting human

[32] http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.htm

[33] Validation involves determining the usefulness and limitations of a test method for a specific purpose. This includes determining the extent that a test method will produce similar results in different laboratories around the world and that the test method can correctly measure or predict the biological effect of interest (see http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf).

and animal health, assessing the need for improved test methods or batteries of test methods to better detect the potential adverse health effects of substances, and identifying opportunities to use alternative test methods to match or improve the protection of human and animal health and the environment while implementing the 3Rs. Interagency collaboration in these areas will maximize efficiency and avoid unnecessary duplication of efforts among the different Federal agencies.

ICCVAM will collaborate with government and non-governmental organizations, where appropriate, to co-sponsor workshops. The objectives of these workshops will be to evaluate the state-of-the-science related to the development and validation of alternative toxicological test methods, and to identify high priority research, development, translation, and validation activities necessary to advance and characterize the usefulness of such methods. The results of these workshops will be broadly communicated to individuals and organizations that conduct such activities.

ICCVAM will foster international collaboration by including experts from the international scientific community on expert panels and workshops. This will ensure that the best international scientific expertise is used to evaluate alternative test methods and provide an opportunity to communicate essential aspects of the ICCVAM test method evaluation process to the international scientific community.

Similarly, NICEATM and ICCVAM will collaborate and share experiences with ECVAM and JaCVAM in the development of international best practices for test method evaluations. These practices include transparency, use of an independent peer review panel, and the opportunity for stakeholder and public comment. Such practices, once developed and adopted internationally, will reduce duplication and streamline efforts while also facilitating the international acceptance of those test methods found to be scientifically valid and acceptable for regulatory testing.

Sidebar: Effective Partnerships

The use of *in vitro* test methods is expected to continue to increase as new science and technologies are incorporated into *in vitro* test methods and such innovative techniques enter the regulatory arena. For this reason, ICCVAM and ECVAM worked together to promote the international application of Good Laboratory Practices (GLPs) to *in vitro* systems by assisting an OECD GLP Working Group of Experts with development of an international guidance document on this subject. With the increasing use of non-animal testing procedures, such guidance directs the acceptable use of these new test methods and the proper generation and documentation of data in accordance with the requirements of GLPs. This will help ensure that *in vitro* data are of acceptable quality for consideration by regulatory authorities. According to ICCVAM, ECVAM, and OECD guidances,

validation studies should ideally be conducted in accordance with GLPs. Thus, a user-friendly, clear, and concise document devoted to the application of GLPs to *in vitro* methods also should encourage the use of GLPs for validation studies, thereby facilitating and increasing confidence in the validation of *in vitro* test methods.

(end sidebar text)

NICEATM and ICCVAM will strengthen international relationships with appropriate organizations to foster the validation and evaluation of alternative test methods. For example, NICEATM and ICCVAM will work with other national and international validation organizations (for example, ECVAM and JaCVAM) to promote ICCVAM's validation and acceptance criteria, which have been substantially incorporated into OECD Guidance Document 34[34]*, and to consider other issues related to validation as they occur. As appropriate, NICEATM and ICCVAM will also participate in the development of performance standards for international test guidelines. To further ensure the development of scientifically valid international test guidelines, NICEATM and ICCVAM will seek to increase participation of its scientists in U.S. delegations to OECD test guideline meetings, expert consultations, and workshops. Additionally, where appropriate, NICEATM and ICCVAM will invite representatives from international organizations such as OECD and from OECD member countries to attend and participate in relevant NICEATM and ICCVAM-sponsored workshops, peer reviews, and other scientific activities.* This provides an opportunity to promote information exchange and scientifically sound test method evaluation processes and principles.

NICEATM and ICCVAM will also engage interested stakeholders in assessing how to efficiently meet Federal peer review requirements, and will seek input on ways to streamline processes that will not compromise transparency, scientific rigor, or the opportunity for stakeholder participation.

The overall aims of these partnerships are to best utilize existing resources and scientific expertise, maximize the efficiency of evaluation/validation efforts, minimize duplication of effort, and ensure an early exchange of information concerning test method validation. This in turn can be expected to facilitate national and international recognition, acceptance, and implementation of scientifically valid test methods.

Monitoring Progress

ICCVAM and NICEATM have a number of mechanisms in place for providing periodic updates to the public. These include the ICCVAM Biennial Progress

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[34] http://appli1.oecd.org/olis/2005doc.nsf/linkto/env-jm-mono(2005)14

Report, the ICCVAM and NICEATM website, and periodic meetings of SACATM. *NICEATM and ICCVAM will also create a web-based database of the 185 test methods that have been reviewed or that are currently undergoing review (see **Appendix F**).* This database will provide transparency for interested stakeholders regarding alternative test methods.

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A full listing of all ICCVAM publications can be found on the NICEATM-ICCVAM website at http://ntp-apps.niehs.nih.gov/iccvampb/searchDoc.cfm

Glossary of Terms[35]

Accuracy: (a) The closeness of agreement between a test method result and an accepted reference value. (b) The proportion of correct outcomes of a test method. It is a measure of test method performance and one aspect of "relevance" and is a term that is often used interchangeably with "concordance".

Acute toxicity[36]: Adverse effects occurring within a short time (usually up to 14 days) after administration of a single dose (or exposure to a given concentration) of a test substance or after multiple doses (exposures), usually within 24 hours; OR the ability of a substance to cause adverse effects within a short time of dosing or exposure.

Assay: The experimental system used. Often used interchangeably with "test" and "test method".

Biological products or Biologics: Includes a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, therapeutic antibodies, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids, or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

Biomarker[37]: A distinctive biological or biologically derived indicator (as a biochemical metabolite in the body) of a process, event, or condition (as aging, disease, or exposure to a toxic substance).

Chronic Toxicity: Adverse effects following chronic exposure; OR effects which persist over a long period of time whether or not they occur immediately upon exposure or are delayed.

Concordance: The proportion of all chemicals tested that are correctly classified as positive or negative. It is a measure of test method performance and one aspect of "relevance". The term is often used interchangeably with "accuracy".

Endpoint: The biological or chemical process, response, or effect assessed by a test method.

Hazard: The potential for an adverse health or ecological effect. A hazard potential results only if an exposure occurs that leads to the possibility of an adverse effect being manifested.

***In vitro*:** Outside the living body and in an artificial environment: "growth of cells *in vitro*", "*in vitro* studies".

***In vivo*:** In the living body of a plant or animal: "*in vivo* synthesis of DNA",

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[35] Unless otherwise indicated, definitions are from ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods (NIH Publication No. 03-4508, September 2003, available at: http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.pdf)

[36] From National Library of Medicine Toxicology Glossary (http://sis.nlm.nih.gov/enviro/iupacglossary/frontmatter.html)

[37] From Medline Plus Medical Dictionary (http://www.nlm.nih.gov/medlineplus/mplusdictionary.html)

"microorganisms are not ordinarily destroyed *in vivo* by bacteriostatic drugs".

Mechanistically based methods: Methods that provide a direct relationship between the biological effects observed and the biological effects of interest.

Performance: The accuracy and reliability characteristics of a test method (see "accuracy", "reliability").

Reduction alternative: A new or modified test method that reduces the number of animals required.

Reference species: The species used in the reference (or traditional) test method to which a new or modified test is being compared. This may be the target species when it is also the species of interest, or it may be a surrogate species when it is not possible to perform testing on the target species.

Reference test method: The accepted *in vivo* test method used for regulatory purposes to evaluate the potential of a test substance to be hazardous to the species of interest.

Refinement alternative: A new or modified test method that refines procedures to lessen or eliminate pain or distress in animals or enhances animal well-being.

Relevance: The extent to which a test method correctly predicts or measures the biological effect of interest in humans or another species of interest. Relevance incorporates consideration of the "accuracy" or "concordance" of a test method.

Reliability: A measure of the degree to which a test method can be performed reproducibly within and among laboratories over time. It is assessed by calculating intra- and inter-laboratory reproducibility and intralaboratory repeatability.

Replacement alternative: A new or modified test method that replaces animals with nonanimal systems or one animal species with a phylogenetically lower one (for example, a mammal with an invertebrate).

Risk: The probability or degree of concern that exposure to an agent will cause an adverse effect in the species of interest.

Risk assessment[38]: Evaluation of the potential adverse health and environmental effects to a target species from exposures to certain substances.

Screen/screening test: A rapid, simple test conducted for the purposes of a general classification of substances according to general categories of hazard. The results of a screen generally are used for preliminary decision-making and to set priorities for more definitive tests. A screening test may have a truncated response range (for example, be able to reliably identify active chemicals but not inactive chemicals).

Substitute method: A new or modified test method proposed for use in lieu of a currently used test method, regardless of whether that test method is for a definitive, screening, or adjunct purpose.

Test: The experimental system used; used interchangeably with "test method" and "assay".

[38] Modified from Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (NIH Publication No. 97-3981, March 1997, available at: http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf)

Test method: A process or procedure used to obtain information on the characteristics of a substance or agent. Toxicological test methods generate information regarding the ability of a substance or agent to produce a specified biological effect under specified conditions. Used interchangeably with "test" and "assay". See also "validated test method" and "reference test method".

Test method nomination: Test methods proposed to ICCVAM for review and evaluation for which a complete test method submission is not available. Four examples are (1) test methods for which adequate validation studies presumably have been completed but lack a complete submission package; (2) test methods that appear promising based on limited revalidation or validation data and are proposed for additional validation studies; (3) test methods that have been developed and are proposed for revalidation or validation studies; and (4) test methods that are recommended for a workshop or other activity.

Test method nominator: The organization or individual that submits a test method nomination to ICCVAM for consideration.

Test method sponsor: The organization or individual that puts forward a test method submission to ICCVAM for consideration.

Test method submission: A test method proposed to ICCVAM for consideration for which adequate validation studies have been completed to characterize the usefulness and limitations of the test method for a specific proposed regulatory testing requirement or application, and adequate documentation of the scientific validity has been prepared in accordance with ICCVAM test method submission guidelines.

Toxicology[39]**:** The study of the adverse effects of chemicals on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning of humans, animals, or the environment.

Transferability: The ability of a test method or procedure to be accurately and reliably performed in different laboratories.

Translation: For the purposes of this document, ICCVAM considers translation as activities that are carried out to characterize if there is evidence of relevance and applicability of a test method for a specific testing purpose. If so, then the test method may be considered for evaluation in a formal validation study.

Validated test method: An accepted test method for which validation studies were conducted and the demonstrated relevance and reliability were sufficient for the test method's intended purpose.

Validation: The process by which the reliability and relevance of a procedure are established for a specific purpose.

[39] Modified from Medline Plus Medical Dictionary (http://www.nlm.nih.gov/medlineplus/mplusdictionary.html)

Acronyms and Abbreviations

3Rs	Replacement, reduction and refinement alternatives in animal testing
ATSDR	Agency for Toxic Substances and Disease Registry
C. elegans	Caenorhabditis elegans
CEBS	Chemical Effects in Biological Systems
CPSC	Consumer Product Safety Commission
DOD	U.S. Department of Defense
DOE	U.S. Department of Energy
DOI	U.S. Department of the Interior
DOT	U.S. Department of Transportation
ECVAM	European Centre for the Validation of Alternative Methods
EPA	U.S. Environmental Protection Agency
FAQ	Frequently Asked Question
FDA	U.S. Food and Drug Administration
FETAX	Frog Embryo Teratogenesis Assay - Xenopus
GLP	Good Laboratory Practice
HTS	High Throughput Screening
IACUC	Institutional Animal Care and Use Committee
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ILSI	International Life Sciences Institute
ISO	International Standards Organization
JaCVAM	Japanese Center for the Validation of Alternative Methods
LLNA	Murine Local Lymph Node Assay
NCI	National Cancer Institute
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development

OSHA	Occupational Safety and Health Administration
PHS	Public Health Service
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
ToxCast	Suite of computer modeling tools for prioritizing chemicals for toxicology testing, developed by the U.S. EPA
UDP	Up-and-Down Procedure
USC	United States Code
USDA	U.S. Department of Agriculture

Appendix A ICCVAM: Mission, Vision, and Strategic Priorities

Background

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) held a strategic planning meeting on January 7-8, 2004 at the National Institutes of Health in Bethesda, MD. The purpose of this meeting was to set the strategic direction of ICCVAM for the next three years. This document provides a concise overview of that direction.

ICCVAM's Mission and Vision

Mission[40]: ICCVAM's mission is to facilitate development, validation and regulatory acceptance of new and revised regulatory test methods that reduce[41], refine[42], and replace[43] the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.

Vision: ICCVAM will:

- Be recognized as a leading authority on test method development and validation both within the federal government and internationally
- Play a leading role in
  - Promoting high quality science as the basis of national and international regulatory policy
  - Setting and harmonizing international standards for scientific validation of test methods
  - Promoting and facilitating the development of priority alternative test methods
  - Identifying key alternative test methods and strategies and facilitating their validation and acceptance
  - Fostering humane and ethical approaches to testing that replace, reduce, and refine the use of animals
  - Promoting awareness and adoption of scientifically validated test methods by regulatory agencies both nationally and internationally
- Develop the internal and collaborative capacity to:
  - Ensure the scientific quality and integrity of its work
  - Implement reliable processes and operating procedures that are credible, effective and efficient
  - Build national and international partnerships with governmental and non-governmental groups, including academia, industry, advocacy groups, and other key stakeholders
  - Secure the necessary human and financial resources to effectively carry out its

[40] All of ICCVAM's activities are grounded in the U.S. Principles for the Utilization and Care of Vertebrate Animal Used in Testing, Research, and Training http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples

[41] Reduction alternative: New or modified test method/s that reduce/s the number of animals required for a test method, while remaining consistent with sound scientific practices necessary to obtain valid results.

[42] Refinement alternative: New or modified test method/s that refine/s procedures to lessen or eliminate pain or distress in animals or enhances animal well-being.

[43] Replacement alternative: New or modified test method/s that replace/s animals with non-animal systems or replace/s an animal species with a phylogenetically lower species.

mission

Central Challenge

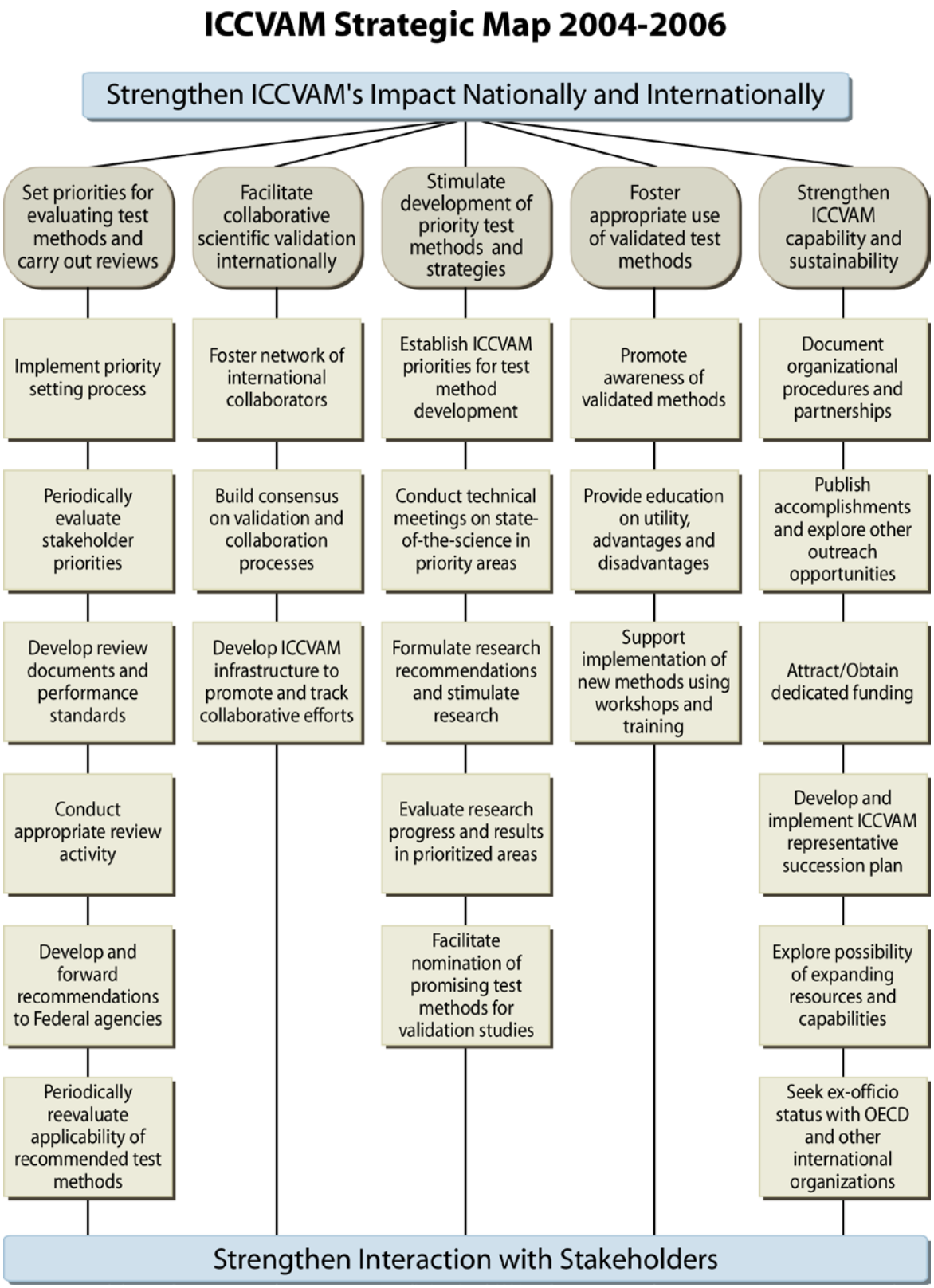
From 2004 through 2006, the central challenge that the ICCVAM faces is to strengthen ICCVAM's impact nationally and internationally.

Strategic Priorities

The following strategic priorities have been established in order to meet the central challenge:

- Set priorities for evaluating test methods and carry out the reviews
- Facilitate collaborative scientific validation internationally
- Stimulate development of priority test methods and strategies
- Foster appropriate use of validated test methods
- Strengthen ICCVAM capability and sustainability
- Strengthen interaction with ICCVAM stakeholders

A Strategic Map (see figure below) and rationale for each strategic priority, its supporting objectives, and the accountabilities for implementation are detailed in the pages that follow.


ICCVAM Strategic Map 2004-2006
Strengthen ICCVAM's Impact Nationally and Internationally
Set priorities for evaluating test methods and carry out reviews
Facilitate collaborative scientific validation internationally
Stimulate development of priority test methods and strategies
Foster appropriate use of validated test methods
Strengthen ICCVAM capability and sustainability
Implement priority setting process
Foster network of international collaborators
Establish ICCVAM priorities for test method development
Promote awareness of validated methods
Document organizational procedures and partnerships
Periodically evaluate stakeholder priorities
Build consensus on validation and collaboration processes
Conduct technical meetings on state-of-the-science in priority areas
Provide education on utility, advantages and disadvantages
Publish accomplishments and explore other outreach opportunities
Develop review documents and performance standards
Develop ICCVAM infrastructure to promote and track collaborative efforts
Formulate research recommendations and stimulate research
Support implementation of new methods using workshops and training
Attract/Obtain dedicated funding
Conduct appropriate review activity
Evaluate research progress and results in prioritized areas
Develop and implement ICCVAM representative succession plan
Develop and forward recommendations to Federal agencies
Facilitate nomination of promising test methods for validation studies
Explore possibility of expanding resources and capabilities
Periodically reevaluate applicability of recommended test methods
Seek ex-officio status with OECD and other international organizations
Strengthen Interaction with Stakeholders

STRATEGIC PRIORITY 1

Set priorities for evaluating test methods and carry out reviews

Rationale: ICCVAM's ability to fulfill its legislative mandate requires that it function with both effectiveness and efficiency. This priority sets specific objectives to ensure ICCVAM's effectiveness, including implementation of the priority setting process that has already been developed and periodic evaluation of the priorities of its stakeholders. In addition, this priority includes objectives to ensure that ICCVAM continues to carry out quality reviews while improving its timeliness and efficiency in doing so.

Objectives:

- Implement ICCVAM's priority setting process
- Periodically evaluate stakeholder priorities
- Develop review documents and performance standards
- Conduct appropriate review activities
- Develop and forward recommendations to federal agencies
- Periodically re-evaluate applicability of recommended test methods

Accountability: ICCVAM
NICEATM

STRATEGIC PRIORITY 2

Facilitate collaborative scientific validation internationally

Rationale: ICCVAM's effectiveness in validating alternative test methods that replace, reduce and refine the use of animals in testing requires it to engage in a wide range of international collaborations. These collaborations provide the basis for ICCVAM to ensure sound science serves as the foundation for validating alternative methods, to promote broad use of validated alternative methods, and to encourage the harmonization of scientific approaches to validation and review.

Objectives:

- Foster a network of international collaborators
- Build consensus on validation and collaboration processes
- Develop ICCVAM infrastructure to promote and track collaborative efforts

Accountability: ICCVAM
NICEATM

STRATEGIC PRIORITY 3

Stimulate development of priority test methods and strategies

Rationale: Test methods must be developed and validated in order for them to be evaluated by ICCVAM. This priority outlines key objectives that ICCVAM needs to carry out in order to stimulate the development of test methods and testing strategies by others. It identifies actions ICCVAM will take to establish priorities for test method development, stimulate method development in prioritized areas, and facilitate the nomination of promising test methods.

Objectives:

- Establish ICCVAM priorities for test method development
- Conduct technical meetings on state of the science in priority areas
- Formulate research recommendations and stimulate research
- Evaluate research progress and results in prioritized areas
- Facilitate nomination of promising test methods for validation studies

Accountability: ICCVAM
NICEATM

STRATEGIC PRIORITY 4

Foster appropriate use of validated test methods

Rationale: Achieving ICCVAM's goal of replacing, reducing, and refining the use of animals in testing requires that validated test methods achieve widespread appropriate use. This priority and its supporting objectives outline key actions that ICCVAM will take to promote the awareness of those validated methods, educate key stakeholders on their appropriate use, and provide support for their effective implementation.

Objectives:

- Promote awareness of validated methods
- Provide education on utility, advantages, and disadvantages
- Support implementation of new methods using workshops and training

Accountability: ICCVAM
NICEATM

STRATEGIC PRIORITY 5

Strengthen ICCVAM capability and sustainability

Rationale: This priority recognizes that ICCVAM's ability to carry out its legislative mandate requires both strong core capability and sustainable resource support. ICCVAM's success in implementing this strategic plan is dependent on the human and financial resources available to support the plan. As a result, this priority and its supporting objectives set forth efforts to obtain dedicated funding, explore the possibility of expanding resources and capabilities, and ensure the effective succession of ICCVAM agency representatives. In addition, this priority also includes ongoing efforts to ensure that ICCVAM develops effective organizational processes and operating procedures.

Objectives:

- Document organizational procedures and partnerships
- Public accomplishments and explore other outreach opportunities
- Attract/obtain dedicated funding
- Develop and implement ICCVAM representative succession plan
- Explore possibility of expanding resources and capabilities
- Seek Ex-Officio status with OECD and other international organizations

Accountability: ICCVAM
NICEATM

STRATEGIC PRIORITY 6

Strengthen interaction with ICCVAM stakeholders.

Rationale: This cross-cutting strategic priority recognizes that effective interaction with stakeholders is an essential component of implementing each of ICCVAM's strategic priorities. Strengthening interaction with stakeholders will help ICCVAM:

- Improve its effectiveness and efficiency in setting priorities for evaluating test methods and carrying out reviews
- Develop international collaborations that promote sound science in validating alternative methods and encourage broad use of validated alternative methods
- Stimulate others to develop test methods and strategies in prioritized areas
- Promote the awareness of validated methods among key stakeholders and provide implementation support for their appropriate use
- Build strong base capability and secure sustainable resource support

Accountability: ICCVAM
NICEATM

Appendix B: Federal Agencies and Programs with Authority to Require or Use Toxicological Testing Information

Agency	Substance	Statute	Program
ATSDR	Health effects of exposure to environmental contaminants near hazardous waste sites	Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Superfund Amendments and Reauthorization (SARA)	Division of Toxicology and Environmental Medicine
CPSC	Consumer product exposures/Household Substances	Federal Hazardous Substances Act; Consumer Product Safety Act; Poison Prevention Packaging Act	Hazard Assessment and Reduction Program and Regulated Products Program
DOI	Drug and chemical management for fisheries	Fish and Wildlife Coordination Act; Federal Insecticide and Fungicide and Rodenticide Act (FIFRA); Federal Food, Drug and Cosmetic Act (FFDCA)	Chemical-Drug Registration Program, U.S. Geological Survey
	Non-Toxic Shot Program	Migratory Bird Treaty Act	Office of Migratory Bird Management, Fish and Wildlife Service
DOT	Exposure to hazardous materials in transport	Federal Hazardous Materials Transportation Law	Pipeline and Hazardous Materials Safety Administration
EPA	Pesticides	FIFRA	Office of Pesticide Programs (OPP)
	Industrial chemicals	Toxic Substances Control Act	Office of Pollution Prevention and Toxics (OPPT)
FDA	Biologicals	FFDCA; Public Health Service Act	Center for Biologics Evaluation and Research
	Medical devices; radioactive materials	FFDCA	Center for Devices and Radiological Health
	Pharmaceuticals and Biologicals	FFDCA; Public Health Service Act	Center for Drug Evaluation and Research
	Food and color additives, cosmetics	FFDCA	Center for Food Safety and Applied Nutrition
	Veterinary drugs	FFDCA	Center for Veterinary Medicine
OSHA	Worker exposure/ Occupational materials	OSHA	Directorate of Standards and Guidance
USDA	Genetically engineered organisms	Plant Protection Act	Animal and Plant Health Inspection Services (APHIS)
	Veterinary biologicals	Virus, Serum, Toxin Act	APHIS
	Meat and Poultry products for human consumption	Federal Meat Inspection Act; Poultry Products Inspection Act	Food Safety and Inspection Service

*OPP and OPPT can require data. In addition to these, most EPA programs can use toxicity testing data/information for regulatory and other purposes. Under the Clean Air Act, EPA's Office of Air and Radiation (OAR) can issue health effects testing requirements for fuel and fuel additives. This is done on a case-by-case basis as data needs are assessed to address specific situations.

CPSC = Consumer Product Safety Commission; DOE = Department of Energy; DOI = Department of Interior; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; OSHA = Occupational Safety and Health Administration; USDA = U.S. Department of Agriculture

Appendix C Process for Development of the NICEATM-ICCVAM Five-Year Plan

This document, prepared by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), in partnership with relevant Federal agency program offices, describes a five-year plan to:

- Research, develop, translate, and validate new and revised non-animal and other alternative assays for integration of relevant and reliable methods into Federal agency testing programs
- Identify areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the replacement, reduction, and refinement of animal tests, when this is scientifically valid and appropriate

Consistent with all ICCVAM and NICEATM document publications, the process of producing the report was planned from the outset to also allow for transparency and multiple opportunities for public comment consistent with the deadline for providing the report. A timeline was developed to provide six separate opportunities for public comments. This included two opportunities during the early, planning stages of the report and four opportunities for comment on the draft report to be considered before it was finalized.

The timeline also included multiple opportunities for review and comment on the plan by SACATM, a Federally chartered advisory committee for NICEATM and ICCVAM. SACATM includes members from industries (for example, pharmaceuticals, pesticides) regulated by ICCVAM agencies, academic institutions, state government agencies, and at least one member of a national animal protection organization. SACATM was provided two opportunities for comment; one during the planning process and one following the release of the draft report. These opportunities also allowed SACATM to consider public comments provided prior to and during their two public meetings.

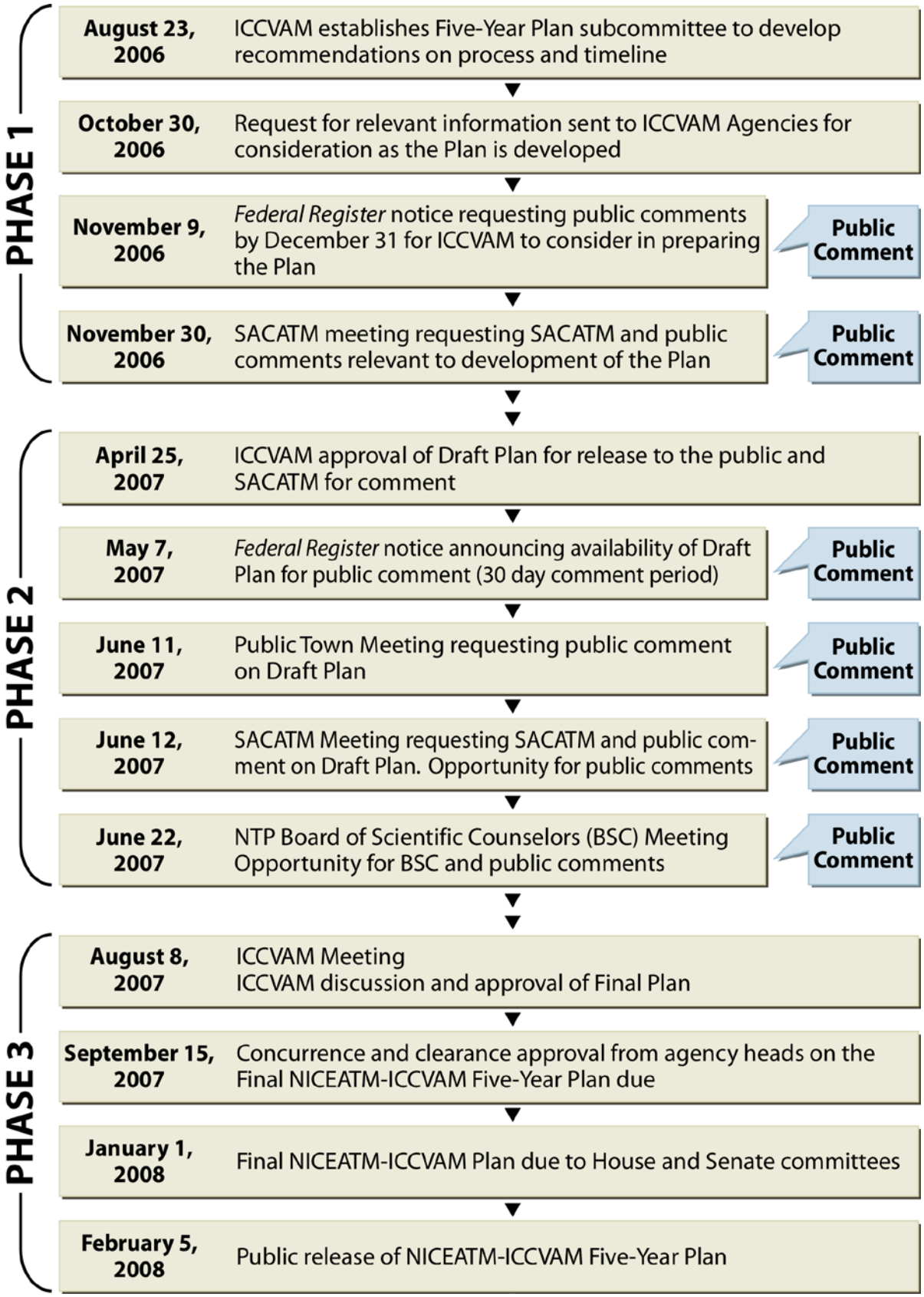
The process for development of the plan included three phases (**Figure 1**). The first phase involved information gathering, during which input was solicited and received from all 15 of the ICCVAM agencies. Specifically, each agency was asked to provide 1) information regarding research, development, translation, validation activities currently in progress or planned during the next five years, and 2) areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the replacement, reduction, and refinement (reduced pain and distress) of animal tests, when this is scientifically valid and appropriate. This initial phase also included requests for comments from the public and SACATM.

During the second phase, an ICCVAM five-year plan subcommittee considered the input received and, in conjunction with NICEATM, prepared an initial draft of the plan for review and comment by the full ICCVAM committee and the 15 ICCVAM agencies. Following this review, comments and suggestions were incorporated into a draft plan released to the public for comment on May 7, 2007. A *Federal Register* notice announcing availability of the draft plan and formally requesting public comment accompanied the release[44]. On June 11, 2007, a town meeting was held specifically to allow an opportunity for public comment. The

[44] both available at http://iccvam.niehs.nih.gov/docs/5yearplan.htm

SACATM met on June 12 to consider and comment on the draft plan and consider comments from the town meeting. The public was provided an additional opportunity to comment during the SACATM meeting.

The final phase of the process involved ICCVAM and NICEATM finalizing the draft plan after taking into consideration public and SACATM comments on the draft plan. The plan was then sent to ICCVAM agency heads for concurrence. NIEHS then forwarded the plan through NIH and the Department of Health and Human Services to the U.S. House of Representatives and U.S. Senate Appropriations Committees. In February 2008, the plan will be released to the public and will be available at the NICEATM and ICCVAM website (http://iccvam.niehs.nih.gov/).


PHASE 1
August 23, 2006
ICCVAM establishes Five-Year Plan subcommittee to develop recommendations on process and timeline
October 30, 2006
Request for relevant information sent to ICCVAM Agencies for consideration as the Plan is developed
November 9, 2006
Federal Register notice requesting public comments by December 31 for ICCVAM to consider in preparing the Plan
Public Comment
November 30, 2006
SACATM meeting requesting SACATM and public comments relevant to development of the Plan
Public Comment
PHASE 2
April 25, 2007
ICCVAM approval of Draft Plan for release to the public and SACATM for comment
May 7, 2007
Federal Register notice announcing availability of Draft Plan for public comment (30 day comment period)
Public Comment
June 11, 2007
Public Town Meeting requesting public comment on Draft Plan
Public Comment
June 12, 2007
SACATM Meeting requesting SACATM and public comment on Draft Plan. Opportunity for public comments
Public Comment
June 22, 2007
NTP Board of Scientific Counselors (BSC) Meeting Opportunity for BSC and public comments
Public Comment
PHASE 3
August 8, 2007
ICCVAM Meeting
ICCVAM discussion and approval of Final Plan
September 15, 2007
Concurrence and clearance approval from agency heads on the Final NICEATM-ICCVAM Five-Year Plan due
January 1, 2008
Final NICEATM-ICCVAM Plan due to House and Senate committees
February 5, 2008
Public release of NICEATM-ICCVAM Five-Year Plan

Appendix D U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training,

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible Institutional Official shall ensure that these principles are adhered to:

I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et. seq.) and other applicable Federal laws, guidelines, and policies.*

II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and *in vitro* biological systems should be considered.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.

V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.

VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.

IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

*For guidance throughout these Principles, the reader is referred to the *Guide for the Care and Use of Laboratory Animals,* prepared by the Institute of Laboratory Animal Resources, National Academy of Sciences.

Published in the *Federal Register* (Vol. 50, No. 97, May 20, 1985), by the Office of Science and Technology Policy

Appendix E The ICCVAM Authorization Act of 2000 (Public Law 106-545, December 19, 2000)

PUBLIC LAW 106–545—DEC. 19, 2000 114 STAT. 2721

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.

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

SECTION 1. SHORT TITLE.

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

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.

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.

(b) PURPOSES.—The purposes of the ICCVAM shall be to—

(1) increase the efficiency and effectiveness of Federal agency test method review;

(2) eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies;

(3) optimize utilization of scientific expertise outside the Federal Government;

(4) ensure that new and revised test methods are validated to meet the needs of Federal agencies; and

(5) reduce, refine, or replace the use of animals in testing, where feasible.

(c) COMPOSITION.—The ICCVAM shall be composed of the heads of the following Federal agencies (or their designees):

(1) Agency for Toxic Substances and Disease Registry.

(2) Consumer Product Safety Commission.

(3) Department of Agriculture.

(4) Department of Defense.

(5) Department of Energy.

(6) Department of the Interior.

(7) Department of Transportation.

(8) Environmental Protection Agency.

(9) Food and Drug Administration.

(10) National Institute for Occupational Safety and Health.

(11) National Institutes of Health.

(12) National Cancer Institute.

(13) National Institute of Environmental Health Sciences.

(14) National Library of Medicine.

(15) Occupational Safety and Health Administration.

(16) Any other agency that develops, or employs tests or test data using animals, or regulates on the basis of the use of animals in toxicity testing.

(d) SCIENTIFIC ADVISORY COMMITTEE.—

(1) ESTABLISHMENT.—The Director of the National Institute of Environmental Health Sciences shall establish a Scientific Advisory Committee (referred to in this Act as the ''SAC'') to advise ICCVAM and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods regarding ICCVAM activities. The activities of the SAC shall be subject to provisions of the Federal Advisory Committee Act.

(2) MEMBERSHIP.—

(A) IN GENERAL.—The SAC shall be composed of the following voting members:

(i) At least one knowledgeable representative having a history of expertise, development, or evaluation of new or revised or alternative test methods from each of—

(I) the personal care, pharmaceutical, industrial chemicals, or agriculture industry;

(II) any other industry that is regulated by the Federal agencies specified in subsection (c);

and

(III) a national animal protection organization established under section 501(c)(3) of the Internal Revenue Code of 1986.

(ii) Representatives (selected by the Director of the National Institute of Environmental Health Sciences) from an academic institution, a State government agency, an international regulatory body, or any corporation developing or marketing new or revised or alternative test methodologies, including contract laboratories.

(B) NONVOTING EX OFFICIO MEMBERS.—The membership of the SAC shall, in addition to voting members under subparagraph (A), include as nonvoting ex officio members the agency heads specified in subsection (c) (or their designees).

(e) DUTIES.—The ICCVAM shall, consistent with the purposes described in subsection (b), carry out the following functions:

(1) Review and evaluate new or revised or alternative test methods, including batteries of tests and test screens, that may be acceptable for specific regulatory uses, including the coordination of technical reviews of proposed new or revised or alternative test methods of interagency interest.

(2) Facilitate appropriate interagency and international harmonization of acute or chronic toxicological test protocols that encourage the reduction, refinement, or replacement of animal test methods.

(3) Facilitate and provide guidance on the development of validation criteria, validation studies and processes for new or revised or alternative test methods and help facilitate the acceptance of such scientifically valid test methods and awareness of accepted test methods by Federal agencies and other stakeholders.

(4) Submit ICCVAM test recommendations for the test method reviewed by the ICCVAM, through expeditious transmittal by the Secretary of Health and Human Services (or the designee of the Secretary), to each appropriate Federal agency, along with the identification of specific agency guidelines, recommendations, or regulations for a test method, including batteries of tests and test screens, for chemicals or class of chemicals within a regulatory framework that may be appropriate for scientific improvement, while seeking to reduce, refine, or replace animal test methods.

(5) Consider for review and evaluation, petitions received from the public that— (A) identify a specific regulation, recommendation, or guideline regarding a regulatory mandate; and (B) recommend new or revised or alternative test methods and provide valid scientific evidence of the potential of the test method.

(6) Make available to the public final ICCVAM test recommendations to appropriate Federal agencies and the responses from the agencies regarding such recommendations.

(7) Prepare reports to be made available to the public on its progress under this Act. The first report shall be completed not later than 12 months after the date of the enactment of this Act, and subsequent reports shall be completed biennially thereafter.

SEC. 4. FEDERAL AGENCY ACTION.

(a) IDENTIFICATION OF TESTS.—With respect to each Federal agency carrying out a program that requires or recommends acute or chronic toxicological testing, such agency shall, not later than 180 days after receiving an ICCVAM test recommendation, identify and forward to the ICCVAM any relevant test method

specified in a regulation or industry-wide guideline which specifically, or in practice requires, recommends, or encourages the use of an animal acute or chronic toxicological test method for which the ICCVAM test recommendation may be added or substituted.

(b) ALTERNATIVES.—Each Federal agency carrying out a program described in subsection (a) shall promote and encourage the development and use of alternatives to animal test methods (including batteries of tests and test screens), where appropriate, for the purpose of complying with Federal statutes, regulations, guidelines, or recommendations (in each instance, and for each chemical class) if such test methods are found to be effective for generating data, in an amount and of a scientific value that is at least equivalent to the data generated from existing tests, for hazard identification, dose-response assessment, or risk assessment purposes.

(c) TEST METHOD VALIDATION.—Each Federal agency carrying out a program described in subsection (a) shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method.

(d) REVIEW.—Not later than 180 days after receipt of an ICCVAM test recommendation, a Federal agency carrying out a program described in subsection (a) shall review such recommendation and notify the ICCVAM in writing of its findings.

(e) RECOMMENDATION ADOPTION.—Each Federal agency carrying out a program described in subsection (a), or its specific regulatory unit or units, shall adopt the ICCVAM test recommendation unless such Federal agency determines that—

(1) the ICCVAM test recommendation is not adequate in terms of biological relevance for the regulatory goal authorized by that agency, or mandated by Congress;

(2) the ICCVAM test recommendation does not generate data, in an amount and of a scientific value that is at least equivalent to the data generated prior to such recommendation, for the appropriate hazard identification, dose-response assessment, or risk assessment purposes as the current test method recommended or required by that agency;

(3) the agency does not employ, recommend, or require testing for that class of chemical or for the recommended test endpoint; or

(4) the ICCVAM test recommendation is unacceptable for satisfactorily fulfilling the test needs for that particular agency and its respective congressional mandate.

SEC. 5. APPLICATION.

(a) APPLICATION.—This Act shall not apply to research, including research performed using biotechnology techniques, or research related to the causes, diagnosis, treatment, control, or prevention of physical or mental diseases or impairments of humans or animals.

(b) USE OF TEST METHODS.—Nothing in this Act shall prevent a Federal agency from retaining final authority for incorporating the test methods recommended by the ICCVAM in the manner determined to be appropriate by such Federal agency or regulatory body.

(c) LIMITATION.—Nothing in this Act shall be construed to require a manufacturer that is currently not required to perform animal testing to perform such tests. Nothing in this Act shall be construed to require a manufacturer to perform redundant endpoint specific testing.

(d) SUBMISSION OF TESTS AND DATA.—Nothing in this Act precludes a party from submitting a test method or scientific data directly to a Federal agency for use in a regulatory program.

Approved December 19, 2000.

LEGISLATIVE HISTORY—H.R. 4281 (S. 1495):

HOUSE REPORTS: No. 106–980 (Comm. on Commerce).

SENATE REPORTS: No. 106–496 accompanying S. 1495 (Comm. on Health, Education, Labor, and Pensions).

CONGRESSIONAL RECORD, Vol. 146 (2000):

Oct. 17, considered and passed House.

Dec. 6, considered and passed Senate.

Appendix F: Test Methods Reviewed or Under Consideration by ICCVAM

Toxicity Area	No.	Test Method (No.)	Regulatory Application and ICCVAM Recommendations
Acute Systemic Toxicity	3	Up-and-Down Procedure (UDP)	In 2001, recommended as replacement alternative for OECD TG 401, the traditional *in vivo* rodent LD_{50} test for assessing acute oral systemic toxicity, and adopted by OECD as TG 425; in 2003, accepted by U.S. agencies.
		In vitro basal cytotoxicity methods (2)	In 2007, both *in vitro* test methods recommended as reduction alternatives to estimate the starting dose in the UDP and Fixed Dose Procedure (FDP) for assessing acute oral systemic toxicity.
Biologics Testing	23[1]	*In vivo* alternatives *Ex vivo* alternatives *In vitro* cell-based methods *In vitro* enzymatic alternatives	In 2006, various reduction, refinement, and replacement alternatives to the mouse LD_{50} assay for botulinum toxin detection and potency testing reviewed at a NICEATM-ICCVAM/ECVAM-sponsored workshop; future activities recommended.
Developmental Toxicity	1	Frog Embryo Teratogenesis Assay: *Xenopus* (FETAX)	In 2000, reviewed at a NICEATM-ICCVAM sponsored workshop as a reduction or replacement alternative to assess the developmental toxicity of chemicals and mixtures; data gaps and inadequacies identified, future activities recommended.
Endocrine Disruptors	138	*In vitro* androgen receptor (AR) binding (11) *In vitro* AR transcriptional activation (TA) (18)	In 2002, evaluated as screens for identifying potential endocrine-disrupting chemicals, to be included in EPA's Endocrine Disruptor Screening Program; in 2003, report with guidance for protocol standardization and validation studies released; in 2006, revised reference substance list released.
		In vitro estrogen receptor (ER) binding (14) *In vitro* ER TA (95)	Same as for *in vitro* AR assays.
Eye Corrosion/ Irritation	4	Bovine Corneal Opacity and Permeability (BCOP) Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) Isolated Chicken Eye (ICE) Isolated Rabbit Eye (IRE)	In 2007, BCOP and ICE recommended as screening tests for identifying corrosives and severe irritants, with certain limitations; HET-CAM and IRE not recommended for regulatory hazard classification purposes until further developed and evaluated.
Pyrogenicity	5	*In vitro* pyrogenicity	In 2007, *in vitro* pyrogenicity test methods measuring cytokine release from human cells recommended as replacements for the rabbit test, subject to product specific validation, to detect endotoxin contamination in parenteral drugs.
Skin Corrosion	4	Corrositex® EpiDerm™ EPISKIN™ Rat Trancutaneous Electrical Resistance (TER) Assay	In 1999, Corrositex® recommended as a stand-alone assay for evaluating acids, bases, and acid derivatives for DOT; otherwise, recommended as part of a tiered testing strategy; in 2000, accepted by U.S. agencies; in 2006, adopted by OECD as TG 435. In 2002, TER and human skin models (EPISKIN™, EpiDerm™) recommended as part of a tiered testing strategy; in 2004, adopted by OECD as TG 430/431.
Skin Sensitization	7	Murine Local Lymph Node Assay (LLNA) LLNA limit dose approach Non-radiolabeled LLNA methods (5)	In 1999, LLNA recommended and accepted by regulatory agencies as alternative for guinea pig tests for allergic contact dermatitis; in 2002, adopted by OECD as TG 429. LLNA performance standards, LLNA limit dose approach, non-radiolabeled LLNA methods currently under review.
Total	**185**		

No. = Number of methods reviewed in each toxicity area, OECD = Organisation for Economic Co-operation and Development; TG = test guideline.

[1]These methods were reviewed and discussed at an ICCVAM-NICEATM/ECVAM sponsored workshop to review the state-of-the-science and current knowledge of alternatives that may reduce, replace, and refine (less pain and distress) the use of mice for botulinum toxin testing (see: http://iccvam.niehs.nih.gov/methods/biologics/bot_workshop.htm)

Appendix G: Roster of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

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

Consumer Product Safety Commission
• Marilyn L. Wind, Ph.D. (Chair)◆
***** Patricia Bittner, M.S.
* 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..

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.
Office of Pesticides Programs
* Amy Rispin, Ph.D.
* Deborah McCall
OECD Test Guidelines Program
* Jerry Smrchek, Ph.D.

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

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 R. 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, M.D., 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.

NICEATM
William S. Stokes, D.V.M., D.A.C.L.A.M. (Director)
Raymond R. Tice, Ph.D. (Deputy Director)
Debbie McCarley (Assistant to the Director)