UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

BIENNIAL PROGRESS REPORT 2014-2015

Interagency Coordinating Committee on the Validation of Alternative Methods

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ICCVAM 2014-2015 Biennial Progress Report

http://ntp.niehs.nih.gov/go/792570

The ICCVAM Authorization Act of 2000 directed ICCVAM to prepare a progress report on its first anniversary and biennially thereafter. The latest ICCVAM Biennial Progress Report describes ICCVAM and ICCVAM agency activities during the period from January 2014 through December 2015.

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The ICCVAM Biennial Report is prepared by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), with support from the NTP Office of Liaison, Policy, and Review. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

A Message from NIEHS and NTP

The purpose of the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) is to promote safety testing methods that protect human health and the environment while replacing, reducing, and refining animal-based test methods. The National Institute of Environmental Health Sciences' (NIEHS) mission is to discover how the environment affects people in order to promote healthier lives; identifying the most human-relevant tests to characterize hazards presented by chemicals is consistent with that mission. In 2014 and 2015, NIEHS continued to support ICCVAM as a member agency and through the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

NIEHS Director Linda Birnbaum, Ph.D.

We are very proud of the NICEATM and ICCVAM accomplishments summarized in this report, and of the recognition that these accomplishments have received in the broader scientific community. Over the last two years, publications by NICEATM, ICCVAM, and collaborators have described testing approaches with the potential to reduce animal use for identifying potential endocrine disruptors and skin sensitizers and for safety testing of pertussis vaccines. For example, NICEATM and U.S. Environmental Protection Agency (EPA) scientists developed an approach for detecting and measuring estrogen receptor bioactivity that relied on Tox21 and ToxCast data. This approach has been accepted as an alternative to tests required by the EPA Endocrine Disruptor Screening Program, the first accepted use of computational tools to replace a regulatory requirement for animal-based testing and a demonstration of the utility of Tox21 efforts. NICEATM staff were recognized for their contributions to this accomplishment in January 2016 with an NIEHS Merit Award. The efforts of NICEATM Director Warren Casey, Ph.D., to introduce a more systematic review of traditional animal studies as a basis of comparison for new approaches were among his accomplishments

NTP Associate Director John Bucher, Ph.D.

noted when he was recognized by the Society of Toxicology with the 2016 Enhancement of Animal Welfare Award.

We would like to recognize changes in the NICEATM leadership that occurred in 2014 and 2015 and have helped drive these accomplishments. In 2014, Casey officially became NICEATM director after serving as acting director in 2013. In 2015, Nicole Kleinstreuer, Ph.D., was appointed NICEATM deputy director. Kleinstreuer brought expertise in computational toxicology to NICEATM over the last three years as a member of the NICEATM ILS support contract team. In her new role as deputy director of NICEATM, she will continue to lead computational toxicology projects, interact with NICEATM's U.S. and international partners and stakeholders, and serve as an ICCVAM member from NIEHS.

Development, acceptance, and implementation of non-animal testing approaches are poised to become central themes in toxicology over the next few years, and NICEATM and ICCVAM are positioned to play key roles. As we reflect on the accomplishments of the past two years, we are also looking forward to continued progress in these areas.

Linda S. Birnbaum, Ph.D., DABT, ATS
Director, NIEHS and NTP

John R. Bucher, Ph.D., DABT
Associate Director, NTP
Director, Division of the NTP, NIEHS

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NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

A Message from NICEATM and ICCVAM

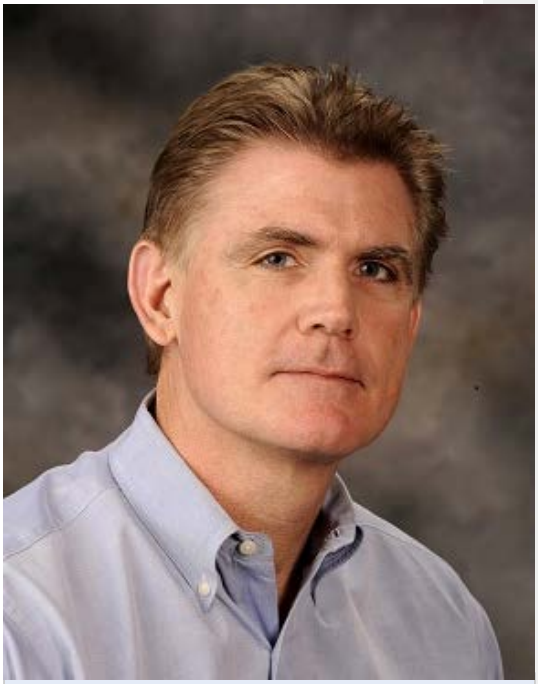
ICCVAM Co-chair Abby Jacobs, Ph.D.

On behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), we are pleased to present the 2014-2015 ICCVAM Biennial Progress Report. This report describes activities of ICCVAM and its 15 member agencies that support the ICCVAM mission of facilitating development, validation, and regulatory acceptance of new testing approaches.

In 2013, ICCVAM advanced a new philosophy under which its activities were to be driven by member agency needs and to better reflect the current direction of the science of toxicology. This report describes outcomes of activities begun under this new philosophy and the significant strides being made. A collaboration between NICEATM and the U.S. Environmental Protection Agency, an ICCVAM member agency, has led to U.S. acceptance of a computational approach that provides a non-animal replacement for a required test. ICCVAM also advanced non-animal testing approaches to identify skin sensitizers. These approaches have the potential to be used by multiple U.S. agencies, and ICCVAM regulatory agencies are currently working with their international counterparts to harmonize testing requirements so that these approaches can be adopted worldwide.

ICCVAM continues to work with NICEATM on outreach efforts, both to raise awareness of available alternative methods and to foster partnerships with stakeholders to maximize efficiency of development, validation, and implementation of new methods. During 2014 and 2015, ICCVAM convened two Public Forum meetings and participated in two public meetings of the Scientific Advisory Committee on Alternative

ICCVAM Co-chair Anna Lowit, Ph.D.



NICEATM Director Warren Casey, Ph.D.

Toxicological Methods (SACATM). The Public Forums were each viewed by over 100 webcast viewers and generated productive interactions between ICCVAM representatives and stakeholders. These meetings provided opportunities for ICCVAM agency representatives to present updates on activities, which then allows the SACATM meetings to be a forum for substantive strategic and technical discussions to better leverage the expertise of the SACATM members in advancing the ICCVAM mission. Additionally, in January 2015, ICCVAM presented its first Communities of Practice webinar featuring expert presentations on a current topic in alternative methods development. Interest in this webinar, which attracted over 250 viewers worldwide, prompted organization of a subsequent webinar series and workshop.

At the end of 2015, for the first time since ICCVAM was established, we began to define a process to add a new member agency to the committee. The National Institute of Standards and Technology will bring expertise and interest in measurement science and method validation to ICCVAM's activities. We look forward to their participation in ICCVAM.

We gratefully acknowledge the contributions of the representatives and interagency working group members from the 15 ICCVAM member agencies. We also acknowledge the contributions from NICEATM and its contract staff, the members of SACATM, and our many other stakeholders.

The activities summarized in this report exemplify ICCVAM's ongoing commitment to working with U.S. and international partners to advance the development and acceptance of new scientifically valid test methods that will reduce and eventually replace animal use. We look forward to continued progress and effective interactions with our stakeholders in the coming years.

Abigail Jacobs, Ph.D., Fellow ATS
Co-Chair, ICCVAM
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Anna Lowit, Ph.D.
Co-Chair, ICCVAM
Office of Pesticide Programs within the
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency

Warren Casey, Ph.D., DABT
Director, NICEATM
Administrative Director, ICCVAM
National Institute of Environmental Health Sciences

The ICCVAM Biennial Report is prepared by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), with support from the NTP Office of Liaison, Policy, and Review. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Key NICEATM and ICCVAM Accomplishments and Impact

In 2013, Linda Birnbaum, Ph.D., director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) announced that NIEHS would move forward with a different philosophy toward ICCVAM whereby the partner regulatory agencies would drive ICCVAM's activities. At the same time, NICEATM would expand its scope to provide bioinformatic and computational toxicology support to the NIEHS Division of the NTP and its Biomolecular Screening Branch.

In 2014 and 2015, projects initiated under this new vision began to bear fruit, with potential impact on animal use worldwide.Some key accomplishments include:

- NICEATM and ICCVAM scientists developed a computational approach that integrates several types of data to predict human skin sensitization hazard without using animals.
- The U.S. Environmental Protection Agency (EPA) announced a plan to adopt high throughput screening assays and computational models for detecting and measuring estrogen receptor bioactivity as an alternative for three Tier 1 tests currently used in its Endocrine Disruptor Screening Program to assess estrogen receptor activity.
- NICEATM evaluated computational approaches to correlate in vitro and in vivo dosimetry. To encourage research and collaboration in this area, ICCVAM made in vitro to in vivo extrapolation the topic of its first Communities of Practice webinar; the positive response to the webinar led to a NICEATM-organized webinar series and workshop on the topic.
- NICEATM continues to evaluate data from acute oral and dermal toxicity tests to determine whether data from

Recognition for NICEATM and ICCVAM Accomplishments

NICEATM and EPA scientists developed an approach for detecting and measuring estrogen receptor bioactivity that relied on Tox21 and ToxCast data. This approach has been accepted as an alternative to tests required by the EPA Endocrine Disruptor Screening Program, the first accepted use of computational tools to replace a regulatory requirement for animal-based testing and a demonstration of the utility of Tox21 efforts. NICEATM staff were recognized for their contributions to this accomplishment in January 2016

oral toxicity tests could be used to assign EPA dermal hazard classifications and eliminate the need for separate acute dermal toxicity tests.

- NICEATM worked with ICCVAM member agencies and international partners to organize a series of workshops that produced recommendations on use of an in vitro test with potential to replace animal use for pertussis vaccine testing.

with an NIEHS Merit Award.

next article - "Acute Systemic Toxicity ..."

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ICCVAM Agency Activities 2014-2015

Key NICEATM and ICCVAM Accomplishments and Impact

NICEATM and ICCVAM accomplishments in 2014 and 2015 have potential impact on animal use worldwide.

Acute Systemic Toxicity

Acute systemic toxicity tests identify short-term toxic effects that appear soon after a substance is swallowed, absorbed through the skin, or inhaled. ICCVAM member agencies are evaluating methods that can reduce the number of animals required for acute toxicity testing or replace animal tests with non-animal alternatives.

Biologics and Vaccine Testing

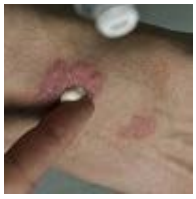
Biologics are products derived from biological sources and used as medicines in humans or animals. ICCVAM agencies are working to identify methods that will refine existing testing procedures or reduce or eliminate the need for animal testing for biologics.

Ecotoxicity Testing

Ecotoxicity testing refers both to the assessment of chemical effects on fish, birds, or other wild organisms and the testing of soil, sediment, or effluents for the presence of toxic compounds. Ecotoxicity testing can require animal testing using either the species of interest or animal models of the species of interest. ICCVAM member agencies are exploring ways to reduce or replace animal use for ecotoxicity studies.

Endocrine Disruptor Testing

Endocrine disruptors include a wide range of compounds that interfere with normal hormone function by mimicking or blocking their action, which may cause adverse health effects. ICCVAM agencies are currently exploring how high throughput screening approaches can be used to identify potential endocrine disruptors without using animals.



Immunotoxicity: Allergic Contact Dermatitis

Allergic contact dermatitis is a skin reaction that may develop in workers and consumers exposed to skin-sensitizing chemicals. Traditional test methods for identifying skin-sensitizing chemicals use guinea pigs or mice, but ICCVAM is developing integrated testing strategies that enable identification of potential skin sensitizers using only in vitro and in silico test data and physicochemical properties.

Ocular Toxicity Testing

Manufacturers test personal care products, household cleaning supplies, and other substances to determine if they could cause temporary or permanent eye damage. ICCVAM scientists participate in evaluations of test methods that assess eye irritation hazard potential without using animals, and ICCVAM agencies have provided guidance on reducing or replacing animal use for this testing.

Photosafety Testing

Photosafety testing is conducted to determine if a topically applied or systemically administered substance will cause a skin reaction after subsequent exposure to light. ICCVAM agencies such as the U.S. Food and Drug Administration are accepting alternative tests to reduce or replace animal use for photosafety testing.

Reproductive and Developmental Toxicity Testing

Reproductive toxicity tests assess a substance's tendency to cause reproductive system effects, while developmental toxicity testing evaluates the extent to which exposure to a substance may harm a developing embryo or fetus. ICCVAM agencies are working with regulatory and industry partners to explore alternative approaches that use fewer animals to make accurate developmental and reproductive safety assessments.

Research and Development Activities Supporting Alternative Methods Development

Many ICCVAM member agencies engage in research activities that focus both on developing new test methods and exploring new technologies that may support future test method development. Effective translation of technological advances into new test methods should allow better protection of public health while addressing animal use and

welfare concerns.

Other ICCVAM Agency Activities Promoting Alternative Methods

In addition to research and validation, ICCVAM agencies are engaged in activities to inform stakeholders about and promote the use of alternative methods.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Acute Systemic Toxicity

All chemicals, drugs, and natural substances are potentially poisonous, or toxic, at high enough doses. Acute systemic toxicity tests identify short-term toxic effects that appear soon after a substance is swallowed (oral toxicity tests), absorbed through the skin (dermal toxicity tests), or inhaled (inhalation toxicity tests). If appropriate, data from acute systemic toxicity tests are used to develop warning labels, protective packaging, occupational personal protective equipment requirements, and environmental release limits.

Traditional acute systemic toxicity tests yield an LD50, or the dose that causes death in 50% of the animals tested. The LD50 is used to categorize toxic substances and determine the hazard classification used on product labels. The currently applied alternatives (up-and-down procedure, acute toxic class method, and fixed dose procedure) reduce the number of animals used for classification and labeling compared to the traditional acute systemic toxicity test. However, ICCVAM member agencies are actively seeking additional methods that can replace these tests with non-animal alternatives or further reduce the number of animals required for acute toxicity testing.

ICCVAM and ICCVAM Agency Activities

- **ICCVAM and National Institute of Environmental Health Sciences**
- **U.S. Department of Defense**
- **National Institute of Environmental Health Sciences and U.S. Environmental Protection Agency**
- **National Institute of Environmental Health Sciences**

Workshop on Alternative Approaches to Acute Systemic Toxicity

This workshop, co-organized by NICEATM, the Physicians Committee for Responsible Medicine, and the PETA International Science Consortium, was held Sept. 24-25, 2015, at the National Institutes of Health in Bethesda, Maryland.

"Key NICEATM and ICCVAM ..." - previous article

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Acute Systemic Toxicity: ICCVAM and NIEHS Activities

EURL ECVAM Evaluation of Methods for Evaluating Human Liver Metabolism and Toxicity

Representatives from NICEATM (National Institute of Environmental Health Sciences) and ICCVAM participated on the management team for a validation study conducted by the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM). The aim of this study was to assess an in vitro test method for evaluating human liver metabolism and toxicity. Advancing novel in vitro test methods for evaluating metabolism and toxicity is a key step in developing in vitro alternatives for in vivo toxicity studies.

The validation study assessed the potential of clinically relevant doses of pharmaceuticals to induce liver enzymes in a human liver cancer cell line (HepaRG®) and cryopreserved primary human liver cells. Liver cytochrome P450 (CYP) enzymes play a major role in biotransformation, the process that converts a substance into a chemically different substance, in humans and other animals. Biotransformation in the liver can potentially increase or decrease chemical toxicity. A stable in vitro model with functional CYP enzyme activity is important for a non-animal assessment of the contribution of biotransformation to toxicity.

The validation study management team issued a draft report on the completed study (2013) in March 2014. The team also contributed to development of the “Draft Proposal for a New Performance Based Test Guideline: Human Cytochrome P450 (CYP) n-fold Induction In Vitro Test Method,” which was made available for comment in July 2015 by the Organisation for Economic Co-operation and Development (OECD). Team members are currently revising the study report and the draft test guideline to address public comments.

Study report and draft test guideline are available on the OECD website.

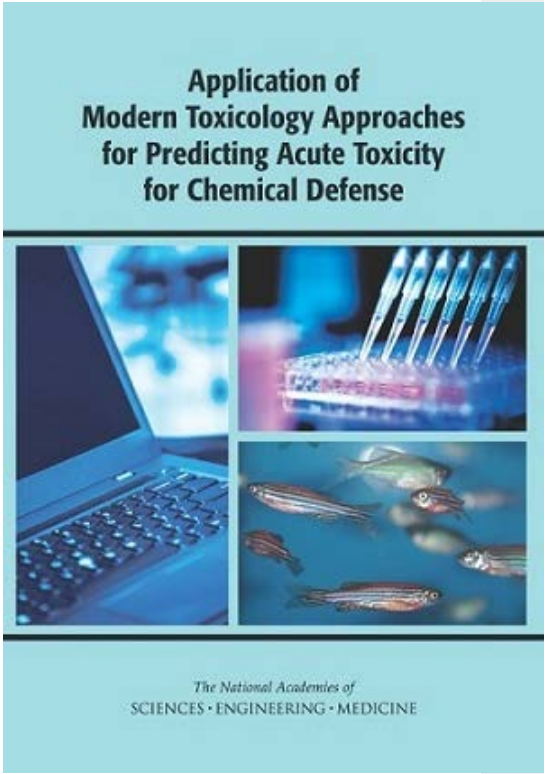
NICEATM ·

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Acute Systemic Toxicity: DOD Activities

Report: Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense

The U.S. Department of Defense (DOD) needs the capability to screen chemicals and predict toxicity and threat status faster, more accurately, and with less reliance on animal use. To further this effort, DOD funded the National Academies of Sciences, Engineering, and Medicine to study how to use modern approaches to predict chemical toxicity. This resulted in the report "Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense." The report reviews the current state of screening methods research and provides findings and recommendations related to these methods and their ability to predict toxicity of chemical threats. The report confirms that DOD could improve its predictive toxicity capability and reduce reliance on animal models; however, this will require further validation of the methods. A dedicated, multi-year investment strategy is needed. Subsequent to this report, DOD is developing an internal roadmap and reaching out to external organizations to discuss opportunities for strategic collaborations.



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Acute Systemic Toxicity: EPA and NIEHS Activities

Use of Data From Oral Toxicity Tests to Determine Dermal Toxicity Hazard Classifications

Data from dermal systemic toxicity tests are used to determine appropriate hazard classification of pesticides and other substances. These categorizations in turn are used to develop product labels and define personal protective equipment requirements for occupational users. NICEATM scientists at the National Institute of Environmental Health Sciences are evaluating data from acute oral and dermal toxicity tests for over 200 pesticide active ingredients, including fungicides, herbicides, and insecticides. The goal is to determine whether data from oral toxicity tests could be used to assign U.S. Environmental Protection Agency (EPA) dermal hazard classifications and eliminate the need for separate acute dermal toxicity tests. Preliminary results presented in a poster (Paris et al.) at the 2015 Annual Meeting of the Society of Toxicology suggest that acute oral toxicity information may provide relevant information on dermal hazard and enable reduction of the number of animals used for dermal acute toxicity testing. The EPA will use a follow-up analysis of nearly 600 pesticide formulations, which produced similar results, to draft guidance for waiving acute dermal toxicity tests for pesticide formulations.

Maull

Acute Systemic Toxicity: NIEHS Activities

Technical Discussion on In Vitro Testing Strategies to Assess Inhalation Toxicity of Nanomaterials

In a June 2014 *Federal Register* (FR) notice (79 FR 35176), NICEATM (National Institute of Environmental Health Sciences) requested available data and information on devices and/or technologies currently used for identifying potential inhalation hazards. Information submitted in response to the FR notice was included in the Technical Discussion on In Vitro Testing Strategies to Assess Inhalation Toxicity of Nanomaterials workshop, organized by NICEATM in cooperation with the PETA International Science Consortium, Ltd., (PISC) on Feb. 24-25, 2015. Attendees at this workshop defined specifications for development and evaluation of an in vitro system to assess inhalation toxicity of multiwalled carbon nanotubes. Recommendations were that the system should include a variety of lung cells co-cultured at an air-liquid interface and consideration of relevant human dosimetry and nanomaterial lifecycle transformations. These recommendations were central to a subsequent request for proposals issued by PISC to develop an appropriate testing system. In September 2015, PISC announced that they would fund groups at the University of Fribourg (Switzerland), Heriot-Watt University (United Kingdom), and MatTek Corporation (U.S.).

Analysis of High Throughput Screening Data to Predict Outcomes of Rat Oral Toxicity Tests

To determine the potential for high throughput screening data to reduce animal use for acute oral toxicity testing, NICEATM analyzed data from Tox21 and the EPA's Toxicity Forecaster (ToxCast™) high throughput screening project for correlation and model fit to rat oral LD50 data. The goal of the analysis was to determine which tests or combinations of tests best characterized the rat oral toxicity data. The analysis, presented in a poster (Polk et al.) at the 2015 Society of Toxicology Annual Meeting, suggests that combinations of in vitro assays and data from small model organisms, such as zebrafish, offer promise for predicting outcomes of rat acute oral toxicity tests.

Workshop on Alternative Approaches for Identifying Acute Systemic Toxicity

The workshop on Alternative Approaches for Identifying Acute Systemic Toxicity: Moving from Research to

Regulatory Testing brought together representatives from regulatory agencies, academia, and industries to develop strategies for advancing alternative methods for product safety testing that meet the needs of regulatory agencies. Workshop attendees defined resources necessary to identify and implement alternatives to animal use, including high-quality reference data, training on use and interpretation of computational approaches, and global harmonization of testing requirements. Breakout groups explored different approaches to reducing or replacing animal use for acute toxicity testing, with each group crafting a roadmap and strategy for accomplishing this within a three-year timeframe. NICEATM will coordinate creation of and provide support for a working group of workshop participants charged with implementing the strategies. Outcomes of the workshop will be summarized in a report to be submitted for publication in 2016.

Participation on European Acute Toxicity Working Team

NICEATM is participating on the Acute Toxicity Working Team of the European Partnership for Alternative Approaches to Animal Testing. This team is investigating methods and data analyses that could replace in vivo acute lethality testing for determining hazard classifications and labeling for new agrochemical and biocide active substances and industrial chemicals. These efforts are aimed at addressing the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation requirements for acute toxicity lethality testing.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Biologics and Vaccine Testing

(Photo courtesy of U.S. Centers for Disease Control)

Biologics are products derived from biological sources and used as medicines in humans or animals. Biologics can include viruses, substances derived from blood and serum, toxins, antitoxins, vaccines, and large polypeptides.

Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA) require batch testing of some biologics. While the specific testing requirements vary among agencies, this testing may be used to develop appropriate labeling, ensure potency of the product when used as labeled, and/or evaluate the safety and potency of manufactured vaccines prior to sale. Some of this testing can use many animals and cause the animals pain and distress. ICCVAM agencies are working to identify methods that will refine existing testing procedures or reduce or replace animal use for biologics testing.

ICCVAM and ICCVAM Agency Activities

- **ICCVAM, National Institute of Environmental Health Sciences, and FDA**: NICEATM worked with ICCVAM member agencies and international partners to organize two workshops to evaluate ongoing studies of alternatives to the murine histamine sensitization test (HIST) for safety testing of acellular pertussis vaccines.

  The first workshop, Progress and Challenges in the Replacement of HIST, was held in August 2014 as a satellite meeting of the Ninth World Congress on Alternatives and Animal Use in the Life Sciences. NICEATM organized the workshop on behalf of the International Working Group for Alternatives to the HIST, a consortium of stakeholders representing government, industry, animal welfare organizations, research and regulatory institutions,

and the European Directorate for the Quality of Medicines and HealthCare (EDQM). At the workshop, consortium scientists reviewed and discussed implementation of in vitro alternatives to the HIST for the testing of acellular pertussis vaccines. The workshop also provided a forum for reviewing the current framework for regulatory acceptance of a harmonized approach for alternative in vitro assays to HIST. A report from this workshop will be published in 2016.

Discussion at the August 2014 workshop laid the groundwork for the March 2015 workshop In Search of Acceptable Alternatives to the Murine Histamine Sensitization Test (HIST): What Is Possible and Practical? This event was organized by NICEATM and the National Centre for the 3Rs (NC3Rs) in collaboration with Health Canada, FDA, EDQM, and the European Union Reference Laboratory for Alternatives to Animal Testing, and was held at NC3Rs in London. Participants in this workshop, including vaccine manufacturers and U.S. and international regulators, evaluated data from a multi-laboratory study that used a Chinese hamster ovary cell-based assay to measure pertussis toxin in reference preparations. Participants concluded that the relevance and reliability of the assay is sufficient, and recommended that vaccine manufacturers begin using the assay alongside current HIST testing to demonstrate its validity for their specific products. Participants also discussed implementing an approach that would allow manufacturers to waive testing entirely under certain circumstances. Regulatory agency representatives attending the workshop agreed in principle to this suggestion. Proceedings from the workshop will be submitted for publication in 2016.

- **FDA**: In June 2015, FDA accepted a cell culture-based assay as an alternative to the mouse LD50 test for potency testing of botulinum neurotoxin drug products. Acceptance of such alternatives is expected to reduce and eventually replace animal use for such testing.
- **USDA**: In April 2015, the USDA Center for Veterinary Biologics (CVB) updated Veterinary Services Memorandum No. 800.112, "Guidelines for Validation of In Vitro Potency Assays." This memorandum provides guidance concerning the information a manufacturer of veterinary vaccines and other biological products should provide when submitting a new potency assay for CVB's consideration. These guidelines apply to in vitro assays used to determine the potency of such products and provide a framework for designing in vitro potency assays and the studies needed to validate those assays. Use of in vitro assays may replace, reduce, or refine

animal use for this purpose.

- **USDA**: In October 2015, CVB issued Notice 15-13, "Option to Remove Back-titration Hamsters from In Vivo Potency Tests for Leptospira Serogroups Canicola and Icterohaemorrhagiae." This notice describes an exemption from the titration requirement in vaccination-challenge potency assays for Leptospira serogroups canicola and icterohaemorrhagiae. The exemption could reduce animal use by 50% for potency testing on these two fractions.

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next article - "Ecotoxicity Testing ..."

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Ecotoxicity Testing

Ecotoxicity testing refers both to the assessment of chemical effects on fish, birds, or other wild organisms and the testing of soil, sediment, or effluents for the presence of toxic compounds. To fulfill their mandates to protect the environment, several ICCVAM member agencies, including the Department of the Interior (DOI) and the U.S. Environmental Protection Agency, require manufacturers of pesticides and other chemical products to conduct ecotoxicity testing.

Ecotoxicity testing can require animal testing using either the species of interest or animal models of the species of interest. ICCVAM member agencies are exploring ways to reduce or replace animal use for ecotoxicity studies.

ICCVAM Agency Activities

- **DOI**: USGS scientists are using a variety of in vitro assay systems for environmental monitoring.

  — USGS scientists are utilizing yeast and mammalian cell assays to monitor endocrine active chemicals in environmental waters. These data along with data from geographic information system analyses are used to identify land uses associated with increased endocrine activity.

  — A suite of yeast, bacterial, and eukaryotic cell culture assays are used to screen environmental waters within National Park Service lands to assess biological activity of chemical mixtures in these waters. This work is done in parallel with comprehensive chemical analysis as a means of assigning possible biological significance.

  — In vitro reporter gene assays and transgenic zebrafish strains

are used to screen water samples for endocrine activity. These include samples from sites near hydraulic fracturing operations, wastewater treatment facilities, and agricultural lands.

— Omics approaches that measure the expression of genes (genomics) or metabolites (metabolomics) are being used in fish to analyze whole organ or individual animal responses to toxicants. For example, studies in carp determined that upregulation of genes involved in uncoupling cellular respiration to energy production is associated with resistance to rotenone. Additionally, metabolomic profiling has been applied to elucidating potential biological pathways influenced by exposure to toxicants. A library of metabolites associated with toxicity to specific toxicants is being developed.

- **DOI**: USGS is developing an approach that reduces animal use for identification of potential fish toxicants by using a more efficient initial screening process. The three integrated phases of the screening process include identifying physical properties of compounds that affect bioavailability in fish, prescreening of a chemical databank to prioritize candidate compounds, and screening of selected compounds for cytotoxicity using in vitro biological assays and fish cell lines. Compounds that demonstrate potent cytotoxic effects are then selected for in vivo biological assays for toxicity screening. Although in vivo testing continues to be utilized, primary investigations using prioritization and in vitro testing reduce the use of whole fish.
  The chemical databank to be used for this purpose is in the final stages of internal review and approval. The databank is expected to be publicly available on the USGS website in the near future.
- **DOI**: Anticoagulant rodenticides, used worldwide for vertebrate pest control in urban and suburban settings, agriculture, and island restoration projects, pose risks to children, companion animals, and nontarget wildlife. As a result, restrictions have been placed on the use of some anticoagulant rodenticide baits.
  Scientists with the U.S. Geological Survey (USGS) and international collaborators have developed an adverse outcome pathway for anticoagulant rodenticides. This effort demonstrated that, while the mechanism of action of anticoagulant rodenticides at the molecular and cellular levels is well understood, future research in specific areas is needed to better characterize the effect of these rodenticides on nontarget species at the individual and population levels.
- **DOI**: Anticoagulant rodenticides are used for rat eradication to

protect breeding colonies of birds on remote island refuges in the Pacific Ocean. USGS is using the up-and-down procedure, as described in EPA guideline OPPTS 870.1100, to reduce animal use for testing the sensitivity of triggerfish to three anticoagulant rodenticides. These studies will help fish and wildlife management biologists determine the relative risks of anticoagulant rodenticide use to nontarget fish species in coral reef areas.

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next article - "Endocrine Disruptor Testing ..."

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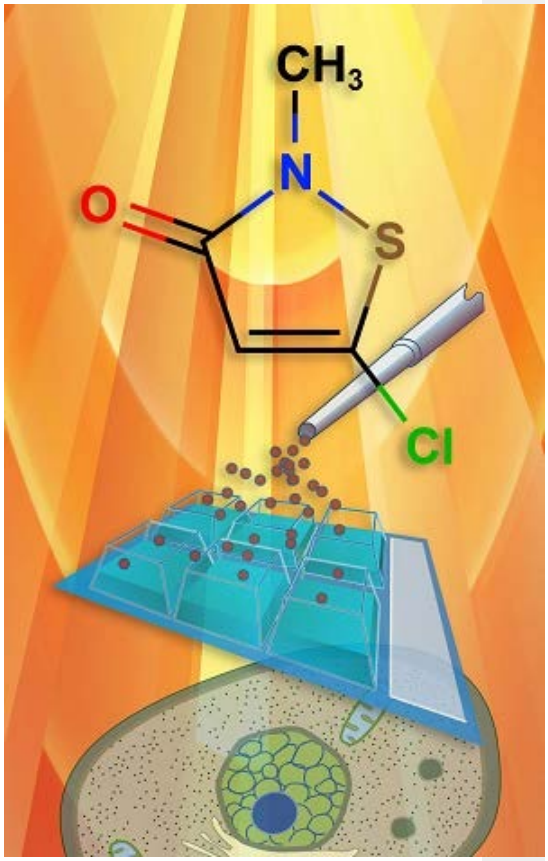
NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Endocrine Disruptor Testing



The endocrine system is one of the body's main communication networks. In the endocrine system, hormones produced by glands throughout the body act as chemical messengers to control a variety of body functions. Examples of hormones include estrogens, androgens, and thyroid hormones.

Endocrine disruptors include a wide range of compounds that interfere with normal hormone function by mimicking or blocking their action, which may cause adverse health effects. Evidence suggests that environmental exposure to endocrine disruptors may cause reproductive and developmental problems in animals; the effect of endocrine disruptors in humans is less clear.

The Food Quality Protection Act of 1996 (7 U.S.C. 136) directed the U.S. Environmental Protection Agency (EPA) to screen pesticides and other substances for their potential to affect the endocrine systems of humans. EPA subsequently initiated the Endocrine Disruptor Screening Program (EDSP) and began efforts to standardize and validate test methods to include in the program. In support of these efforts, ICCVAM sponsored reviews of and validation studies on test methods proposed to identify potential endocrine disruptors.

ICCVAM agencies are currently exploring how high throughput screening (HTS) approaches can be used to identify potential endocrine disruptors without using animals.

ICCVAM and ICCVAM Agency Activities

- ICCVAM, National Institute of Environmental Health Sciences, and U.S. Environmental Protection Agency
- U.S. Environmental Protection Agency

- National Institute of Environmental Health Sciences and U.S. Environmental Protection Agency
- National Institute of Environmental Health Sciences

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Endocrine Disruptor Testing: ICCVAM and ICCVAM Agency Activities

Reference Data for In Vitro Androgen Receptor Assays

Using a list of putative androgen-active or inactive chemicals for which Tox21 or ToxCast data were available, NICEATM (National Institute of Environmental Health Sciences) performed a literature search to identify in vitro androgen receptor (AR) assay data. Posters describing the literature search were presented at the 2015 Annual Meeting of the American Society of Cellular and Computational Toxicology (Kleinstreuer et al.) and the 2015 Society of Toxicology FutureTox III meeting (Kleinstreuer et al.). In concert with this effort, the U.S. Environmental Protection Agency is conducting a literature search for in vivo assay data on androgenic activity on the same chemicals. ICCVAM established a working group in 2015 to review data from these literature searches with the goal of defining a list of reference chemicals and associated potencies for future validation of Tox21/ToxCast results and other novel AR assays.

Endocrine Disruptor Testing: EPA Activities

Update of EDSP Comprehensive Management Plan

The U.S. Environmental Protection Agency (EPA) updated the Comprehensive Management Plan (2014) for the Endocrine Disruptor Screening Program (EDSP) to emphasize the use of advanced informational technology and computational methods. The updated plan provides strategic guidance for agency personnel and outlines the critical EDSP activities that are planned over the next five years. Among these activities is a focus on using informational technology to enhance data interpretation and apply computational methods to more efficiently prioritize and screen chemicals in the EDSP for potential endocrine bioactivity.

Acceptance of High Throughput Screening Tests to Replace Current EDSP Tier 1 Tests

In a June 2015 *Federal Register* notice (80 FR 35350), EPA requested comments on a plan to accept ToxCast/Tox21 high throughput screening (HTS) assay data and an associated computational model as an alternative to three EDSP Tier 1 tests used to assess estrogen receptor activity. Described as "groundbreaking" in an EPA press release, the use of HTS assays and computational methods will accelerate the pace of screening, decrease costs, and reduce animal testing. The EPA approach was developed and validated by EPA and NICEATM scientists and is described in detail in a paper in Environmental Science and Technology.

More information about EPA's use of high throughput assays and computational tools in EDSP

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Endocrine Disruptor Testing: NIEHS and EPA Activities

Development of Domain-specific QSAR Models for Estrogenic Activity

NICEATM (National Institute of Environmental Health Sciences) is working with scientists at the U.S. Environmental Protection Agency (EPA) and the University of North Carolina at Chapel Hill to develop domain-specific quantitative structure-activity relationship (QSAR) models using data from Tox21 and ToxCast assays. For example, the team developed QSAR models to predict specific activity and relative potency of phenolic compounds that act on the estrogen pathway. The domain-specific models consistently yielded higher balanced accuracy, sensitivity, and specificity than models that considered all possible chemical structures. Posters describing these models were presented at the 2015 American Society for Cellular and Computational Toxicology (ASCCT) Annual Meeting (Mansouri et al.) and the 2015 Society of Toxicology (SOT) FutureTox III meeting (Mansouri et al.).

Computational Model for Prediction of Androgenic Activity

Data from nine Tox21 and ToxCast assays were integrated into a computational model that predicts androgen receptor (AR) agonist and antagonist bioactivity. The preliminary results from this model were presented at the December 2014 meeting of the EPA Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel. The model is currently undergoing refinement.

QSAR Model to Predict Androgen Receptor Binding Activity

Using data from nine Tox21 and ToxCast assays, NICEATM is developing a QSAR model to predict AR binding activity, with the goal of using the model to predict AR pathway activity for chemicals being evaluated in the EPA Endocrine Disruptor Screening Program. Posters describing the model were presented at the 2015 SOT Annual Meeting (Zang et al.), 2015 ASCCT Annual Meeting (Zang et al.) and 2015 SOT FutureTox III meeting (Zang et al.).

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Endocrine Disruptor Testing: NIEHS Activities

Validation of High Throughput Assay for Estrogen-Active Chemicals

NICEATM (National Institute of Environmental Health Sciences) compared the quality and accuracy of a quantitative high throughput screening (HTS) assay to measure estrogen agonist or antagonist activity in human cells with the manual method validated for regulatory use by the U.S. Environmental Protection Agency and described in Test Guideline 455 issued by the Organisation for Economic Co-operation and Development (OECD). The comparison indicated that the performance of the HTS method is equivalent to the manual method.

Curated Database of Rodent Uterotrophic Bioactivity

The uterotrophic assay measures the estrogenic activity of a chemical by assessing the chemical's effect on the weight of a rodent uterus. To support future validation of in vitro HTS methods and in silico models of estrogenic activity, NICEATM created a comprehensive database of high quality in vivo data from over 1,000 scientific articles describing uterotrophic assay experiments performed using over 2,660 different chemical/study/protocol combinations. These data have potential utility for developing adverse outcome pathways or models of estrogenic activity, prioritizing chemicals for further testing, or evaluating species-specific responses to chemicals. The database is available on the NICEATM website.

Models for Correlation of In Vitro and In Vivo Dosimetry

Using collective results from 16 Tox21 and ToxCast estrogen receptor pathway related assays, NICEATM developed and applied one-compartment or physiologically based pharmacokinetic models to quantitatively correlate in vitro and in vivo dosimetry for estrogen receptor reference chemicals. This approach highlighted the importance of considering the entire process of absorption, distribution, metabolism, and excretion in assessing and ranking endocrine-active chemicals based on in vitro HTS assays. A manuscript describing this project was published in December 2014 in Applied In Vitro Toxicology, and posters describing an approach to optimize parameters in these analyses were presented at the 2015 Society of Toxicology (SOT) Annual Meeting (Chang et al.), 2015 American Society for Cellular and Computational Toxicology (ASCCT)

Annual Meeting (Chang et al.), and 2015 SOT FutureTox III meeting (Chang et al.).

Review of Assays to Identify Thyroid-Active Chemicals

NICEATM scientists contributed to development of the report "New Scoping Document on In Vitro and Ex Vivo Assays for the Identification of Modulators of Thyroid Hormone Signalling." This 2014 report, developed by the OECD Expert Group on Amphibian Testing and the OECD Validation Management Group on Non-animal Testing, provides recommendations for development and use of existing in vitro and ex vivo thyroid assays and identifies data gaps that require development of additional tests.

The scoping document and other OECD documents on endocrine disruptor testing are available on the OECD website.

Computational Methods to Assess Similarity of In Vitro Bioactivity

NICEATM used computational methods to create clusters of tested chemicals based on their activity in ToxCast assays. Clusters containing known toxicants were examined to identify similar in vitro bioactivity patterns in environmental chemicals lacking in vivo data. This work was described in a platform presentation at the 2015 SOT Annual Meeting and is being included as a case study in a manuscript on good read-across practices being prepared in collaboration with the Johns Hopkins University Center for Alternatives to Animal Testing and other partners from industry, government, and academia.

Validation Study of In Vitro Method for Androgen Receptor Activity

NICEATM is collaborating with the test method developer CertiChem, Inc., on a proof-of-concept evaluation of an in vitro test method that uses MDA-Kb2 cells to measure androgen receptor agonist and antagonist activity. Testing of this medium throughput method using a blinded set of chemicals was completed in October 2015. Data are currently being analyzed and a manuscript describing these results is planned.

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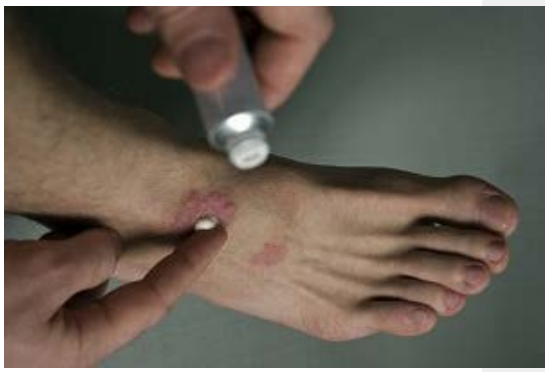
Immunotoxicity: Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) may develop in workers and consumers exposed to skin-sensitizing chemicals and products, which include chemicals such as formaldehyde, formulations such as pesticides, and metals such as nickel. To prevent such exposure, regulatory agencies require the testing of chemicals and products to determine their potential to cause ACD.

The traditional test methods for detecting ACD hazard potential of chemicals use guinea pigs. As alternatives to guinea pig tests, ICCVAM has recommended various versions and applications of the murine local lymph node assay (LLNA). The LLNA eliminates pain and distress experienced by the test animal, requires less time to perform, uses fewer animals, and provides dose-response information.

While the LLNA has advantages over guinea pig methods, it is still an animal-based test. Accordingly, ICCVAM is developing integrated testing strategies that enable identification of potential skin sensitizers using only in vitro and in silico test data and physicochemical properties.



Allergic Contact Dermatitis

Allergic contact dermatitis is a skin reaction characterized by localized redness, swelling, blistering, or itching after direct contact with a skin allergen such as poison ivy.

ICCVAM and ICCVAM Agency Activities

- ICCVAM and National Institute of Environmental Health Sciences
- U.S. Consumer Product Safety Commission
- National Institute of Environmental Health Sciences

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Immunotoxicity Testing: ICCVAM and NIEHS Activities

Development of an Integrated Testing Strategy for Prediction of Skin Sensitization Hazard

NICEATM and ICCVAM scientists developed an integrated testing strategy that uses data from three in vitro tests (the direct peptide reactivity assay, human cell line activation test, and KeratinoSensTM assay), six physicochemical properties, and an in silico read-across prediction of skin sensitization hazard as inputs to machine-learning approaches to predict murine local lymph node assay (LLNA) outcomes and human skin sensitization hazard. Using a particular combination of inputs and machine-learning approaches (computer algorithms that can make predictions or decisions about sets of data) yielded more accurate predictions of LLNA or human skin sensitization hazard than any of the in chemico, in vitro, or in silico methods alone. Three manuscripts describing different strategies and targets will result from these efforts. One has been accepted for publication in the Journal of Applied Toxicology; the other two will be submitted in 2016.

ICCVAM Evaluation of the Electrophilic Allergen Screening Assay

The electrophilic allergen screening assay, an in chemico method, was nominated to ICCVAM in 2012 for evaluation of its usefulness to identify potential skin sensitizers. NICEATM has been working with the test method sponsor to address technical issues with the assay prior to advancing to a validation study.

suggestions to NICEATM.

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Immunotoxicity Testing: CPSC Activities

Update of "Strong Sensitizer" Definition"

In 2014, the U.S. Consumer Product Safety Commission (CPSC) issued a final rule updating the Federal Hazardous Substances Act to clarify the definition of “strong sensitizer” as the term applies to substances and products that CPSC regulates. The revised definition eliminates redundancy, removes certain subjective factors, incorporates new and anticipated technology, defines criteria for “severity of reaction,” and provides for the use of a weight-of-evidence approach to determine whether a substance is a strong sensitizer. The new rule places the criteria for classification of strong sensitizers in the following descending order of importance: well-conducted clinical and diagnostic studies; epidemiological studies, with a preference for general population studies over occupational studies; well-conducted animal studies; well-conducted in vitro test studies; cross-reactivity data; and case histories. The new rule also provides for consideration of quantitative structure-activity relationships (QSAR), in silico data, specific human sensitization threshold values, and other data on potency and sensitizer bioavailability, if data are available and the methods validated.

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Immunotoxicity Testing: NIEHS Activities

Development of an Open-source Bayesian Network for Identification of Potential Skin Sensitizers

NICEATM and other scientists within the National Institute of Environmental Health Sciences (NIEHS) collaborated with scientists at Procter & Gamble (P&G) to develop an integrated testing strategy that can identify potential skin sensitizers and characterize skin sensitization potency without conducting animal tests.

The P&G-developed integrated testing strategy uses a Bayesian network to analyze all available relevant substance information, including non-animal tests, in silico models, and other information such as chemical structure and solubility, to produce a numerical probability of skin sensitization potency. Using the available information, the Bayesian network can identify the subsequent test that will best inform the skin sensitization potency prediction of a substance. The calculated probability could be used to make a hazard labeling decision without animal testing.

The software used by P&G for these analyses is patented, which could limit regulatory implementation of this approach because it is not fully transparent. Accordingly, NIEHS and P&G collaborated to develop an integrated testing strategy that uses open-source software and publicly available data. The code and data used to generate the predictions is available for other researchers to test, verify, and build upon.

The open-source integrated testing strategy was described in a short communication to the journal ALTEX. Subsequent revisions of the approach improved overall accuracy and enabled consideration of variability in reference data. A poster describing improvements to the strategy was presented at the 2015 Society of Toxicology Annual Meeting (Pirone et al.). Other improvements to simplify model inputs and refine potency estimates are described in a paper published in Archives of Toxicology.

Development of QSAR Models to Identify Potential Skin Sensitizers

NICEATM is collaborating with scientists at the University of North Carolina at Chapel Hill to develop

quantitative structure-activity relationship (QSAR) models to support identification of potential human skin sensitizers without using animals. Two papers published in 2015 in Toxicology and Applied Pharmacology described QSAR models developed for skin penetration and to predict results of animal tests to identify sensitizers. More recent efforts have focused on developing QSAR models to predict human skin sensitization; a manuscript describing these models is in preparation.

Collaboration with Cosmetics Europe Skin Tolerance Task Force

NICEATM is collaborating with the Cosmetics Europe Skin Tolerance Task Force to evaluate skin sensitization integrated approaches to testing and assessment (IATAs) that have been submitted to the Organisation for Economic Co-operation and Development. NICEATM has evaluated seven IATAs against a set of previously untested chemicals with in vitro and in silico data provided by Cosmetics Europe. Manuscripts describing the datasets and the outcome of the IATA analyses are in preparation.

Participation on Management Teams for Validation Studies of In Vitro Test Methods

NICEATM scientists participated on management teams for studies to validate two in vitro methods identifying potential skin sensitizers: the IL-8 luciferase skin sensitization assay and the Vitrigel-SST assay. These studies were coordinated by the Japanese Center for the Validation of Alternative Methods. Laboratory work on the studies has been completed and the study results are undergoing peer review.

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Ocular Toxicity Testing

Manufacturers test personal care products, household cleaning supplies, and other substances to determine if they could cause temporary or permanent eye damage. Test results are used to classify these substances using appropriate national and international hazard classification systems. These systems direct how substances must be packaged, labeled, and handled in order to prevent injury to the eyes.

Nearly all of this testing, referred to as ocular toxicity testing, has been conducted using the rabbit eye test. Evaluation of alternatives to animal use for ocular toxicity testing is a high priority for ICCVAM agencies. Past ICCVAM ocular toxicity test method evaluations identified in vitro test methods that could replace animal use in some applications. For applications where animal use is still necessary, ICCVAM recommended approaches to reduce the number of animals used and minimize pain and distress in those animals.

ICCVAM and ICCVAM Agency Activities

- **ICCVAM and National Institute of Environmental Health Sciences (NIEHS)**: NICEATM is coordinating the validation of the in vitro OptiSafe ocular irritation test method. In this method, a test substance is applied to a semipermeable membrane and damage to macromolecules in the membrane is measured to assess the substance's potential to cause eye irritation. NICEATM staff and members of the ICCVAM Ocular Toxicity Working Group will serve on a validation management team to provide oversight and direction for a multilaboratory validation study. Testing should be completed in 2016, along with a study report detailing the results.
- **U.S. Environmental Protection Agency (EPA)**: In March 2015, EPA updated its guidance document describing a non-animal testing scheme for assessing eye irritation potential of EPA-registered antimicrobial cleaning products. The testing scheme uses the bovine corneal opacity and permeability, EpiOcular, and cytosensor microphysiometer assays to classify antimicrobial cleaning products as Toxicity Category I (corrosive or severely irritating to the eye), Category II (moderately irritating), and Category III (mildly irritating) without using live animals.
- **NIEHS**: In 2013, NICEATM prepared a summary review document describing their evaluation of data submitted by Kao Corporation, the test method sponsor, in support of the short time exposure (STE)

test. The STE is an in vitro test proposed to identify the eye injury hazard potential of chemicals and products by measuring cultured rabbit corneal epithelial cell viability following test substance exposure.

After an National Toxicology Program-sponsored peer review of the final NICEATM summary review document, Kao Corporation submitted it and other documents to the Organisation for Economic Co-operation and Development (OECD) in 2014 for consideration of the STE as an in vitro alternative to current ocular hazard identification tests. In July 2015, OECD adopted a new Test Guideline 491 describing the use of the STE to identify (1) chemicals inducing serious eye damage and (2) chemicals not requiring eye hazard classification.

- **NIEHS**: NICEATM scientists participated on management teams for two validation studies of in vitro methods to identify potential eye irritants, the SIRC-CVS assay and the Vitrigel-EIT assay coordinated by the Japanese Center for the Validation of Alternative Methods. Laboratory work on the Vitrigel-EIT assay is in progress; study results on the SIRC-CVS assay are undergoing peer review.

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Photosafety Testing

Photosafety testing is conducted to determine if a topically applied or systemically administered substance will cause a skin reaction after subsequent exposure to light. Traditionally, animals have been used to evaluate photosafety. ICCVAM agencies such as the U.S. Food and Drug Administration (FDA) are accepting alternative tests to reduce or replace animal use for photosafety testing.

ICCVAM and ICCVAM Agency Activities

- **FDA:** In January 2015, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), of which FDA is a member, issued the guidance document "S10 Photosafety Evaluation of Pharmaceuticals." The ICH guidance outlines details on when photosafety testing is warranted and on possible assessment strategies, including in vitro test methods that might be useful. The purpose of the guidance is to harmonize such assessments that support human clinical trials and marketing authorization for pharmaceuticals, and to avoid international duplication of studies.

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next article - "Reproductive and Developmental Toxicity ..."

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Reproductive and Developmental Toxicity Testing

Pesticides, food additives, drugs, and other substances are tested for their potential to cause reproductive or developmental toxicity. Reproductive toxicity tests assess a substance's tendency to cause reproductive system effects, while developmental toxicity testing evaluates the extent to which exposure to a substance may harm a developing embryo or fetus.

Reproductive and developmental toxicity tests are required by multiple regulatory agencies and can use large numbers of animals. The complexity of these endpoints makes it unlikely that any single alternative test method will serve all regulatory needs. ICCVAM agencies are working with regulatory and industry partners to explore alternative tests that can be used in combination to provide the information needed to make accurate developmental and reproductive safety assessments.

ICCVAM Agency Activities

- **National Institute of Environmental Health Sciences:** NICEATM is working with other National Toxicology Program scientists to establish a list of reference chemicals for use in validation studies of alternative test methods for developmental toxicity. The list is being constructed with input from experts from industry, academia, and government and is expected to include a broad variety of chemicals, including agrochemicals and pharmaceuticals, that have been shown to have either positive or negative activity in clinical pharmaceutical studies or high-quality in vivo developmental toxicity studies in rodents or rabbits. The identified reference chemicals will be candidates for evaluating the performance of in vitro assays based on primary cells, stem cells, or cell lines, as well as in vivo assays using lower order organisms such as zebrafish or the roundworm Caenorhabditis elegans.

- **National Institute of Environmental Health Sciences:** NICEATM scientists participated on the management team for a validation study coordinated by the Japanese Center for the Validation of Alternative Methods to evaluate the Hand-1 luciferase assay, which measures toxicity to mouse embryonic stem cells to identify potential developmental toxicants. Laboratory work on the study is ongoing.

"Photosafety Testing ..." - previous article

next article - "Research and Development Activities ..."

Research and Development Activities Supporting Alternative Methods Development

ICCVAM member agencies work to promote the regulatory acceptance of new, scientifically valid toxicological tests that protect human and animal health and the environment while replacing, reducing, or refining animal tests. To achieve this goal, many ICCVAM member agencies engage in research activities that focus both on developing new test methods and exploring new technologies that may support future test method development. Effective translation of technological advances into new test methods should allow better protection of public health while addressing animal use and welfare concerns.

ICCVAM Agency Activities

- U.S. Department of Defense
- U.S. Environmental Protection Agency (EPA)
- National Institute of Environmental Health Sciences (NIEHS)
- NIEHS, EPA, and U.S. Food and Drug Administration
- Interagency Tox21 Research Initiative

"Reproductive and Developmental Toxicity ..." - previous article

next article - "Other ICCVAM Agency Activities ..."

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Research and Development: DOD Activities

Establishment of the ADMET Center of Excellence

The U.S. Department of Defense (DOD) continues to make investments in alternative non-animal methods to develop medical countermeasures to chemical and biological threats. One such effort has led to establishment of the Absorption, Distribution, Metabolism, Elimination, and Toxicology Center of Excellence (ADMET CoE). The ADMET CoE brings best practices from the pharmaceutical industry to DOD, first assessing potential toxicity and efficacy through modeling and in vitro screening mechanisms and then selecting the most promising clinical candidates. This approach could reduce the reliance on animal models for developing medical countermeasures to chemical and biological threats.

"Human-on-a-chip" Project and XCEL Program

The DOD “human-on-a-chip” project aims to develop a platform that uses microphysiological organ systems to mimic all 10 human physiological systems. The platform allows microphysiological systems to interact with each other in a physiologically relevant manner. Recently, this platform demonstrated four interacting microphysiological systems. In the next phase, the goal is to demonstrate seven interacting organ systems and, by the end of the program, 10 interacting microphysiological systems.

While the “human-on-a-chip” focuses on early screening of medical countermeasures, DOD is independently investing in a five-year collaboration known as the XCEL (Ex Vivo Countermeasure Evolution and Licensure) Program, which focuses on chemical and biological threat agent assessment and medical countermeasure research and development. XCEL consists of two multi-institutional program teams that bring together domestic and international talents and leaders in the field of microphysiological systems research. In XCEL, four human primary cell-based organ systems (liver, heart, lung, and kidney/blood vessel) are being integrated into a platform with support of a universal media (blood surrogate), interlinked microfluidics (channels, pumps and valves), in-line sensors (biomedical,

immunological, chemical, physical and physicoelectrical sensing), and off-line analytics with on-board data integration. The program will develop the incrementally integrated platform over several years: Year 1, liver; Year 2, liver and heart; Year 3, liver, heart, and lung; Year 4, liver, heart, lung, and kidney/vessel; Year 5, partial validation of the platform by live testing with known threat agents and toxic drugs.

Rapid Hazard Screening Program

The DOD Rapid Hazard Screening program focuses on developing new approaches to predict and determine the potential health hazards of new chemicals and materials. The program uses high throughput in vitro assays, zebrafish embryos, transcriptomics, and computational predictive modeling, combined with a biological pathway-based hazard/risk screening framework, to rapidly and accurately determine potential human and ecological health hazards of DOD chemicals and materials. These approaches enable extrapolation from exposure concentrations to assay or tissue-dose concentrations, allowing prediction of exposure levels below which no impact would be expected. The methods and framework should provide more accurate hazard-level screening and reduce animal use for in vivo safety tests required for new chemical development. The hazard/risk decision support framework under development will integrate data from the ADMET CoE, “Human-on-a-chip,” and XCEL programs to enable consistent prediction of adverse health impacts with diverse data sets. The Rapid Hazard Screening program is collaborating with the U.S. Environmental Protection Agency and international organizations such as the Organisation for Economic Co-operation and Development to ensure that the approaches being developed are consistent with national and international efforts.

Phased Approaches to Testing and High Throughput Screening

The ADMET CoE, the “human-on-a-chip,” XCEL, and Rapid Hazard Screening programs are concerted, strategic efforts focused on developing new approaches to reduce the reliance on animal models for DOD’s chemical and biological portfolios. Other efforts are aimed at implementing approaches to reduce DOD’s reliance on animal models using, for example, phased approaches to testing and high throughput screening (HTS). In this approach, new candidate compounds undergo a battery of in silico and in vitro testing early in the development process. This approach allows compounds of concern to be eliminated early in the research, development, testing, or evaluation process, reducing the likelihood of testing in an animal model. Phased acute toxicity testing is built on in vitro data, and limited repeat-dose animal testing is focused on targets of toxicity learned from previous in silico and in vitro tests. One effort underway aims to conduct initial screening for toxicity using established cell lines grown in a monoculture or a co-culture with immune cells for the following organs: lung, liver, skin, brain and kidney. With an HTS approach, up to 10 chemicals at three different concentrations can be screened on a 384-well plate with multiple endpoints for analysis, including cell viability, toxicity, nuclear count, oxidative stress, and ATP levels. A three-dimensional, co-culture system for each of the organs of interest is also under development to screen chemicals for these same endpoints. The use of a three-dimensional culture allows for better approximation of the structure and function of each organ system.

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Research and Development: EPA Activities

ToxCast Program Activities

The ToxCast program generates data and predictive models on thousands of chemicals of interest to the U.S. Environmental Protection Agency (EPA). ToxCast uses HTS methods and computational toxicology approaches to rank and prioritize these chemicals for additional testing that may be needed to fully characterize their hazards. ToxCast program activities during 2014-2015 include:

- Releases of reference data from animal toxicity studies (October 2014) and chemical information and assay results (October 2015)
- Stakeholder workshops in January and April 2014 and the second ToxCast Data Summit in September 2014, which gave stakeholders opportunities to explore ToxCast data and tools and share applications of ToxCast data
- Release of the Interactive Chemical Safety for Sustainability (iCSS) dashboard in September 2014, which provides an interactive tool to explore in vitro high throughput data generated by the ToxCast and Tox21 projects

Funding for Systems-Based Research for Evaluating Ecological Impacts of Manufactured Chemicals

In early 2014, EPA accepted applications for the funding opportunity "Systems-Based Research for Evaluating Ecological Impacts of Manufactured Chemicals." Six grants were awarded to academic laboratories to support development and application of innovative methods and models to better understand biological and ecological consequences of exposure to chemicals. Awardees are developing adverse outcome pathway (AOP) models for effects of chemicals on aquatic species, allowing prediction of adverse effects and possible identification of safer alternatives.

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Research and Development: NIEHS Activities

Workshop on Good Cell Culture Practices for Induced Pluripotent Stem Cells

NICEATM (National Institute of Environmental Health Sciences [NIEHS]) co-organized the Workshop on Good Cell Culture Practices for Induced Pluripotent Stem Cells that was held in Baltimore in June 2015. The goal of this workshop was to develop consensus standards and foster international standardization on the use of induced pluripotent stem cells. Using existing standards for cell and tissue culture systems as a guide, the attendees considered the unique properties and challenges of pluripotent stem cells compared to traditional in vitro systems. Attendees then developed a framework for a guidance document specific to pluripotent stem cells that addresses quality of materials and methods, documentation, protection of workers and the environment from hazards, compliance with laws and ethical principles, and education and training. The guidance document will be submitted for publication in 2016.

Workshop on Adverse Outcome Pathways

NICEATM and the Physicians Committee for Responsible Medicine organized the workshop Adverse Outcome Pathways: From Research to Regulation. Plenary presentations that explained the adverse outcome pathway (AOP) concept and described case studies were followed by breakout sessions that considered AOP applications, development of new AOPs, and challenges to regulatory adoption of AOPs.

Systematic Evaluation of the Application of Zebrafish in NTP Toxicology Studies

NICEATM is part of an National Toxicology Program (NTP) effort, known

Workshop on Adverse Outcome Pathways

The workshop Adverse Outcome Pathways: From Research to Regulation was held in September 2014 at NIH. A report from the workshop will be submitted for publication in 2016.

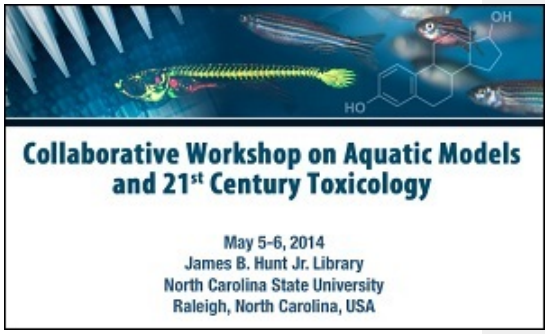
as SEAZIT, to systematically evaluate the application of zebrafish in NTP toxicology studies. This effort will provide fundamental knowledge on the use of zebrafish in toxicology and support further research endeavors by the academic community.

The ICCVAM Biennial Report is prepared by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), with support from the NTP Office of Liaison, Policy, and Review. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Research and Development: NIEHS, EPA, and FDA Activities

Collaborative Workshop on Aquatic Models and 21st Century Toxicology



NICEATM (National Institute of Environmental Health Sciences) collaborated with scientists at North Carolina State University (NCSU), Duke University, the U.S. Environmental Protection Agency (EPA), and the U.S. Food and Drug Administration (FDA) to organize the Collaborative Workshop on Aquatic Models and 21st Century Toxicology. The workshop, held at NCSU in May 2014, examined the use of small fish and fish embryos in medium and high throughput toxicity testing. The event provided a valuable opportunity for researchers within and outside the field of toxicology to share insights on the potential role of small fish and fish embryos in the future of toxicology. Participants identified topics for further exploration, including the effective application of fish study data for better understanding chemical safety and the integration of fish data with complementary information from other types of toxicity studies. Participants noted that the suitability of small fish species for toxicity testing needs to be brought to the attention of other audiences including industry, regulators, scientists in other disciplines, and the general public. A report from the workshop will be submitted for publication in 2016.

Maull | Report Editor: Catherine Sprankle

BIENNIAL PROGRESS REPORT
2014-2015
Interagency Coordinating Committee
on the Validation of Alternative Methods

Research and Development: Tox21 Activities

The interagency Tox21 research initiative uses in vitro high throughput screening (HTS) assays to test a broad variety of substances and considers data from those screens collectively to assess effects on biological pathways related to toxicity. Data from Tox21 testing will be used to develop a better understanding of adverse outcome pathways, enabling the eventual use of in vitro assay data to predict the adverse effects of chemical exposures in vivo. The goals of Tox21 are to efficiently prioritize chemicals for in vivo testing and to use results from validated HTS assays to identify endpoints for targeted in vivo testing.

- A crowdsourcing initiative known as the DREAM Toxicogenetics Collaboration tested how well the effects of a toxic compound could be predicted in different people. Hundreds of computational biologists from all over the world developed approaches to predicting the toxicities of environmental compounds. The collaboration showed that computational methods could be used to predict some toxic effects on populations; however, these methods are not yet sensitive enough to predict such effects in individuals. The collaboration resulted in the development of algorithms useful for environmental risk assessment as well as new methods for improving some areas of hazard evaluation and assessment.
- Scientists from Tox21 partner agencies developed a list of

genes to use for evaluating transcriptional changes in human cells or tissues in response to chemical exposures in a high throughput format. The "S1500+" gene list, containing approximately 2750 genes, was derived through bioinformatic approaches, experimental data, and public nominations. These genes may also be useful for biomarker development and basic research efforts.

More information about Tox21 can be found on participating agencies' websites: NIEHS/NTP, NIH/National Center for Advancing Translational Sciences, and EPA/National Center for Computational Toxicology.

The ICCVAM Biennial Report is prepared by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), with support from the NTP Office of Liaison, Policy, and Review. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Other ICCVAM Agency Activities Promoting Alternative Methods

- **U.S. Environmental Protection Agency (EPA)**: EPA is continuing to expand acceptance of alternative methods for acute toxicity testing for pesticides.

  — In June 2014, EPA staff viewed the webinar "Validation and Utilization of Alternative Test Methods" presented by NICEATM Director Warren Casey, Ph.D. The webinar provided an overview of internationally accepted non-animal methods for identification of substances causing skin or eye irritation. Casey also discussed current efforts to develop integrated testing strategies that use data from multiple sources to arrive at a hazard classification decision for potential skin sensitizers. This approach could reduce or eliminate animal testing for this purpose.

  — In December 2014, EPA published the report "Process for Establishing and Implementing Alternative Approaches to Traditional In Vivo Acute Toxicity Studies," which describes a transparent, stepwise process for evaluating and implementing alternative tests for acute oral, dermal, inhalation toxicity, along with skin and eye irritation and skin sensitization (often referred to as the "six-pack studies"). Included in this report is a discussion of the three major phases of this process and the implications for reporting information under section 6(a)(2) of the Federal Insecticide, Fungicide, and Rodenticide Act.

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

This series of four webinars began in October 2015 and will culminate in a February 17-18, 2016, workshop at the U.S. Environmental Protection Agency in Research Triangle Park, North Carolina.

- **U.S. Food and Drug Administration (FDA)**: FDA convened the workshop, Methods for Thrombogenicity Testing of Medical Devices, on April 14, 2014, at the FDA White Oak Campus in Silver Spring, Maryland. Participants discussed optimizing the conduct of current in vivo tests and the identification of alternative in vitro tests that could provide equivalent or improved clinical insights into the potential for blood clot formation caused by medical devices.
- **National Institute of Environmental Health Sciences and EPA**: NICEATM and EPA are co-organizing a webinar series and workshop on In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making. The webinars and workshop aim to address the capabilities and limitations of in vitro to in vivo extrapolation (IVIVE) within the context of risk decision making. The webinar series will present the current state of the science and the in-person workshop will facilitate discussions that follow up and build on information presented in the webinars. Workshop participants will (1) review the state of the science to form recommendations on the best practices for using IVIVE in chemical screening and risk decision making, (2) identify areas that require additional data and/or research, and (3) highlight examples of how best to apply IVIVE in a tiered risk decision-making strategy.
- **National Library of Medicine (NLM)**: In 2014, the NLM updated the Hazardous Substances Data Bank (HSDB), a part of NLM's Toxicology Data Network (TOXNET®), to enhance its records for chemicals and substances. Improvements include the creation of new subheadings in the human and non-human toxicity excerpts to allow users to more efficiently locate data from in vitro and other alternative methods. Coverage includes results from methods validated by ICCVAM and the European Union Reference Laboratory for Alternatives to Animal Testing.

"Research and Development Activities ..." - previous article

next article - "Immunotoxicity Testing: CPSC Activities ..."

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Outreach and Collaborative Activities

ICCVAM strengthened its ties with U.S. and international collaborators in 2014 and 2015 by sponsoring meetings and webinars, by collaborating with other national validation organizations, and by attending national and international workshops and scientific meetings.

Public Forums

ICCVAM held two public forum meetings in 2014 and 2015. These meetings provided an opportunity for public interaction with representatives from the 15 ICCVAM member agencies.

Communities of Practice Webinar

ICCVAM initiated a series of “Communities of Practice” webinars in 2015 to provide opportunities for detailed consideration of a current topic relevant to alternative test method development.

International Cooperation on Alternative Test Methods

The International Cooperation on Alternative Test Methods (ICATM) was established in 2009 to promote consistent and enhanced voluntary international cooperation, collaboration, and communication among national validation organizations.

ICCVAM Contributions to OECD Activities

ICCVAM member agencies participate in the development and national review of guidelines for the testing of chemicals issued by the Organisation for Economic Co-operation and Development (OECD). OECD test guidelines can be used by government, industry, and independent laboratories in OECD member countries to determine the safety of chemical preparations.

Advisory Committee Meetings

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory group that advises NICEATM, ICCVAM, and the NIEHS director about ICCVAM activities. SACATM held public meetings in September 2014 and September 2015.

ICCVAM Participation at National and International Meetings

NICEATM and ICCVAM scientists participated in a number of workshops, conferences, and meetings in 2014 and 2015. This section includes brief descriptions of selected events.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Public Forums

ICCVAM held its first public forum on June 25, 2014, at the National Institutes of Health (NIH) in Bethesda, Maryland. This meeting was attended by over 50 individuals in person and remotely and provided an opportunity for public interaction with representatives from the 15 ICCVAM member agencies. ICCVAM representatives provided information about their agencies' activities relevant to the development and use of alternative test methods. These ranged from near-term solutions (product-specific validation of non-animal methods) to longer-term, more complex approaches (organs-on-a-chip) to predict hazards to human health and the environment and minimize animal use.

The 2015 public forum was held on May 27 at NIH in Bethesda. Twelve public participants and nearly 100 webcast viewers joined 15 ICCVAM representatives from 10 member agencies. Highlights of activities presented by seven ICCVAM member agencies included a description of how the U.S. Environmental Protection Agency (EPA) is working with pesticide producers to implement alternative tests or waive tests completely, and a National Institute of Environmental Health Sciences (NIEHS) summary of how non-animal methods were used to rapidly assess health hazards presented by the January 2014 Elk River chemical spill in West Virginia.

Key points raised by commenters at both meetings included requests for more transparency in reporting animal use by industry and more training for regulators on available non-animal methods and strategies. One commenter at the 2015 forum also emphasized the need for better communication to the public on the science behind non-animal methods.

ICCVAM Public Forum Meetings

- View materials from the 2014 Public Forum
- View materials from the 2015 Public Forum

next article - "Communities of Practice Webinar ..."

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Communities of Practice Webinar

ICCVAM initiated a series of “Communities of Practice” webinars in 2015 to provide opportunities for detailed consideration of a current topic relevant to alternative test method development. The first, presented on Jan. 27, 2015, was titled “Reverse Toxicokinetics: Using In Vitro Data to Estimate Exposures That Could Be Associated With Adverse Effects In Vivo.” The webinar, which attracted over 250 viewers, focused on the development and application of reverse toxicokinetic models for extrapolation of high throughput screening data to in vivo dosimetry. Presenters provided an overview of the development of reverse toxicokinetic models and discussed the consideration of population variability and sensitive subpopulations when using these models. NICEATM and EPA’s National Center for Computational Toxicology hosted the webinar on behalf of ICCVAM. Interest in the webinar prompted organization of a subsequent webinar series and workshop.

ICCVAM Communities of Practice Webinars

- View materials from the January 2015 webinar, "Reverse Toxicokinetics: Using In Vitro Data to Estimate Exposures That Could Be Associated With Adverse Effects In Vivo"
- View materials from the January 2016 webinar, "Fundamentals of Using Quantitative Structure-Activity Relationship Models and Read-across Techniques in Predictive Toxicology"

"Public Forums ..." - previous article

next article - "International Cooperation on Alternative ..."

provide NICEATM with a copy for our records. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

International Cooperation on Alternative Test Methods

The International Cooperation on Alternative Test Methods (ICATM) was established in 2009 to promote consistent and enhanced voluntary international cooperation, collaboration, and communication among national validation organizations. The goals of ICATM are to:

- Ensure optimal design and conduct of validation studies
- Ensure high-quality independent scientific peer reviews of alternative test methods
- Ensure consistent and transparent stakeholder involvement
- Achieve greater efficiency and effectiveness by internationally leveraging limited resources and avoiding duplication of effort
- Support the timely international adoption of alternative test methods

This cooperation enables scientifically valid alternative methods or strategies to be more readily accepted worldwide for regulatory use.

ICATM includes member organizations (see sidebar) from the European Union, United States, Japan, Canada, and South Korea. Brazil and China began participating in ICATM in 2015 as observers, with plans to join as full members in 2016.

ICATM meetings take place several times a year and provide an opportunity for the five organizations to discuss activities in identified areas of cooperation. These regular interactions allow ICATM partners to develop good communications and working relationships in support of collaborative test method development. ICCVAM representatives participated in three ICATM coordination meetings in 2014 and 2015.

ICCVAM Collaborations With International Validation Organizations

- Representatives from EURL ECVAM, JaCVAM, KoCVAM, and

ICATM Participant Organizations

- **ICCVAM** is an interagency committee of the U.S. government that coordinates technical reviews of alternative test methods and cross-agency activities relating to validation, acceptance, and harmonization of test methods. NICEATM administers ICCVAM and provides scientific support for its activities.
- **EURL ECVAM** (European Union Reference Laboratory for Alternatives to Animal Testing) is a unit within the Institute of Health and Consumer Protection in the European Union's Joint Research Centre. EURL ECVAM coordinates the

Health Canada attended the 2014 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods as nonvoting liaisons.

- EURL ECVAM has liaisons to the ICCVAM Skin Sensitization and Ocular Toxicity Working Groups; EURL ECVAM and KoCVAM have liaisons to the ICCVAM Acute Toxicity Working Group. EURL ECVAM, JaCVAM, KoCVAM, and Health Canada have liaisons to the ICCVAM Androgen Receptor Reference Chemical Working Group.
- ICCVAM nominated experts to participate on EURL ECVAM Scientific Advisory Committee peer reviews of in vitro skin sensitization and ocular toxicity test methods.
- NICEATM or ICCVAM scientists participated on the management teams for the following validation studies coordinated by international partners during 2014 and 2015.

Toxicity Area	Test Method	Coordinating Organization
Acute toxicity	In vitro test method for evaluating human liver metabolism and toxicity	EURL ECVAM
Immunotoxicity: allergic contact dermatitis	IL-8 luciferase skin sensitization assay	JaCVAM
Immunotoxicity: allergic contact dermatitis	Vitrigel-SST method for identifying potential skin sensitizers	JaCVAM
Ocular toxicity	Rabbit cornea derived cell line (SIRC-CVS) assay for identification of ocular irritants	JaCVAM
Ocular toxicity	Vitrigel-EIT method for identifying potential eye irritants	JaCVAM
	Hand-1 luciferase assay for	

validation of alternative test methods in the European Union.

- **JaCVAM** (Japanese Center for the Validation of Alternative Methods) coordinates the evaluation of alternative test methods for the Japanese National Institute of Health Sciences, its parent organization.
- **Health Canada's** Environmental Health Science and Research Bureau coordinates the evaluation of alternative test methods in Canada.
- **KoCVAM** (Korean Center for the Validation of Alternative Methods) is part of the National Institute of Food and Drug Safety Evaluation of the South Korean Food and Drug Administration.

Reproductive and developmental toxicity	identification of substances with potential embryotoxicity	JaCVAM

"Communities of Practice Webinar ..." - previous article

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ICCVAM Contributions to OECD Activities

ICCVAM member agencies participate in the development and national review of guidelines for the testing of chemicals issued by the Organisation for Economic Co-operation and Development (OECD). OECD test guidelines represent internationally agreed-upon testing methods that can be used by government, industry, and independent laboratories in the 34 OECD member countries to determine the safety of chemicals and chemical preparations.

The U.S. National Coordinator for the OECD Test Guidelines Programme, an ex officio member of ICCVAM, solicits and collates U.S. comments on draft test guidelines and other documents of the Test Guidelines Programme. The National Coordinator represents the United States at the annual meeting of the National Coordinators of the Test Guidelines Programme and in other test guideline development activities. During 2014-2015, first Christine Olinger and then Wanda Hall, both of the U.S. Environmental Protection Agency (EPA), served as U.S. National Coordinator.

Judy Strickland, Ph.D., senior toxicologist on the ILS NICEATM support contract, attended a November 2014 meeting of the OECD expert group tasked with drafting the "Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment ." Strickland submitted for inclusion in the draft guidance document a case study of the ICCVAM integrated decision strategy that uses machine-learning approaches to predict skin sensitization. The draft guidance document and case studies are under review by the OECD Task Force on Hazard Assessment.

ICCVAM co-chairs Anna Lowit, Ph.D., of EPA and Abby Jacobs, Ph.D., of the U.S. Food and Drug Administration (FDA) along with ICCVAM member Suzanne Fitzpatrick, Ph.D., of FDA attended the November 2015

OECD
BETTER POLICIES FOR BETTER LIVES

More Information about OECD

- OECD Test Guidelines Programme
- Adopted OECD test guidelines

OECD-sponsored workshop Framework for the Development and Use of Integrated Approaches to Testing and Assessment in Arlington, Virginia. The workshop's objectives were to discuss how the adverse outcome pathway (AOP)/mode-of-action concept could be used to develop and refine integrated approaches for testing and assessment, and define the degree of confidence needed to apply these to specific regulatory contexts. A report from the workshop was published by OECD in July 2015.

NICEATM Director Warren Casey, Ph.D., and ICCVAM member Patience Browne, Ph.D., EPA, attended a December 2015 meeting of the OECD Validation Management Group-Non-animal in Budapest, Hungary. This international group focuses on evaluation of new methods for identifying endocrine disruptors. Casey led a discussion on selection of reference chemicals for evaluating these new methods, and Browne gave two presentations, one focused on evaluating estrogenic activity of environmental chemical metabolites, and one on the status of a pathway-based validation approach. The group also discussed current proposals for the use of high throughput methods for identifying endocrine disruptors.

"International Cooperation on Alternative ..." - previous article

next article - "Advisory Committee Meetings ..."

Advisory Committee Meetings

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory group that advises NICEATM, ICCVAM, and the Director of the National Institute of Environmental Health Sciences (NIEHS) about ICCVAM activities. SACATM held public meetings on September 16, 2014, and September 2, 2015, at NIEHS in Research Triangle Park, North Carolina.

At the 2014 meeting, ICCVAM Co-chair Anna Lowit, Ph.D., Environmental Protection Agency (EPA), presented an update of new ICCVAM procedures and summarized EPA's progress toward expanding the use of in vitro methods and reducing animal use in pesticide testing. Joanna Matheson, Ph.D., Consumer Product Safety Commission, discussed the ICCVAM Skin Sensitization Working Group's review of in vitro skin sensitization test methods evaluated by the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) and the working group's progress in developing an integrated testing strategy for skin sensitization. NICEATM Director Warren Casey, Ph.D., provided an update on NICEATM activities and also described ICCVAM activities to improve stakeholder communication. He and Lowit gave a presentation summarizing international interactions and clarifying differences in structure, activities, and mission among the member organizations of the International Cooperation on Alternative Test Methods. ICCVAM Co-chair Abby Jacobs, Ph.D., Food and Drug Administration (FDA), briefed SACATM on ICCVAM's goals for 2015 and identified acute systemic toxicity, skin sensitization, adverse outcome pathways (AOPs), international coordination, and new paradigms for validation as priority areas. Jacobs also updated SACATM on FDA activities contributing to reductions in animal use in drug and biologics testing. NICEATM and ICCVAM members provided summaries

More Information about SACATM

Materials from past SACATM meetings

Federal Register notices announcing SACATM meetings:

- September 2014 meeting
- September 2015 meeting

Roster of SACATM members during 2014 and 2015

of workshops on aquatic models, AOPs, and replacement of the murine histamine sensitization test for pertussis vaccine testing. Updates on 3Rs activities were provided by David Dix, Ph.D. (EPA); Nigel Walker, Ph.D. (NIEHS); Barnett Rattner, Ph.D. (Department of the Interior), and Carol Clarke, D.V.M. (U.S. Department of Agriculture [USDA]).

The 2015 SACATM meeting was structured to put more emphasis on substantive discussion of challenging topics relevant to the 3Rs. To that end, SACATM was given an opportunity to discuss three broad questions relevant to the advancement of animal alternatives: international harmonization of animal testing requirements, measurement of success in the 3Rs, and creation of a U.S. roadmap for alternative methods development. Brief updates on ongoing 3Rs activities were provided by Dix (EPA), Clarke (USDA), and Richard McFarland, Ph.D. (FDA). Casey and Lowit also presented brief updates on NICEATM and ICCVAM activities. An NIEHS presentation described funding opportunities available for small businesses developing alternative methods.

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The ICCVAM Biennial Report is prepared by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), with support from the NTP Office of Liaison, Policy, and Review. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

ICCVAM Participation at National and International Meetings

NICEATM and ICCVAM scientists participated in a number of workshops, conferences, and meetings in 2014 and 2015. Brief descriptions of selected events are listed in the table below. References for poster presentations and some platform presentations are listed on the Biennial Report publications page.

Please note that any conclusions and recommendations issued in the proceedings of the meetings outlined below are those of the meeting participants. The inclusion of these conclusions and recommendations in this report should not be interpreted as an endorsement by ICCVAM or any of its member agencies.

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Meeting Date and Location	Sponsoring Organization	Meeting Title and Description	Summary of ICCVAM or ICCVAM Agency Activity
Jan.16-17, 2014 Chapel Hill, North Carolina	Society of Toxicology	**FutureTox II: Pathways to Prediction** The Society of Toxicology (SOT) organized the FutureTox meeting series to address the topic of transforming	NICEATM scientists contributed to five posters describing use of high throughput screening data and computational methods to predict endocrine activity and skin sensitization

		21st century science into risk assessment and regulatory decision-making.	potential of chemicals. A report of the workshop was published in February 2015 in Toxicological Sciences.
Feb. 27, 2014 Somerset, New Jersey	New Jersey Association of Biomedical Research	**3Rs Sharing Conference** This conference focused on the topic "Paving the Path to Regulatory Acceptance of Alternative Methods: Facilitating the Integration of Alternative Methods Into the Regulatory Framework." The conference included speakers from the pharmaceutical and chemical industries who presented case studies and strategies for effective safety testing using fewer animals.	NICEATM Director Warren Casey, Ph.D., presented the keynote address, "New Direction and Transformation of NICEATM and ICCVAM."
March 24-27, 2014 Phoenix, Arizona	Society of Toxicology	**53rd Annual Meeting**	ICCVAM Co-chair Abby Jacobs, Ph.D., U.S. Food and Drug Administration (FDA), co-chaired a session on non-animal approaches to photosafety testing of pharmaceuticals. NICEATM and ICCVAM scientists contributed to 15 poster presentations describing non-animal, high throughput, and

			computational approaches to chemical safety assessment.
Aug. 24-28, 2014 Prague, Czech Republic	World Congress on Alternatives and Animal Use in the Life Sciences	**Ninth World Congress on Alternatives and Animal Use in the Life Sciences**	NICEATM scientists presented nine posters and three talks on topics including development of curated reference databases and computational and high throughput approaches to chemical screening and toxicity. ICCVAM committee members from the National Institute of Environmental Health Sciences (NIEHS) and FDA co-chaired five sessions and gave six platform presentations.
Dec. 2-5, 2014 Arlington, Virginia	U.S. Environmental Protection Agency (EPA)	**Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel** This panel, composed of experts from government and academia, provides independent scientific advice to EPA on a wide range of health and safety issues related to pesticides.	Casey and Nicole Kleinstreuer, Ph.D., senior staff computational toxicologist on the ILS NICEATM support contract, presented on the curation of a uterotrophic assay database and a plan for use of high throughput screening data to replace three Tier 1 tests of the Endocrine Disruptor Screening Program (EDSP). The EPA considered the panel's feedback in its

			June 2015 proposal to replace three current EDSP Tier 1 tests with validated ToxCast/Tox21 high throughput assays and an associated computational model.
Feb. 10-12, 2015 Baltimore, Maryland	OpenTox Association	**OpenTox USA 2015** The theme of this conference was "Driving the Big Science Challenge in Safety Forward."	Kleinstreuer presented a summary of NICEATM activities supporting development of an integrated testing strategy for skin sensitization.
March 22-26, 2015 San Diego, California	Society of Toxicology	**54th Annual Meeting**	ICCVAM members from FDA, EPA, and NIEHS co-chaired four sessions, and Casey gave two platform presentations. NICEATM staff members were co-authors on 11 posters presented at the meeting, and ICCVAM members were co-authors on six posters describing alternative testing methods and strategies.
April 2, 2015 and June 4, 2015 Washington, DC	National Research Council	**Meetings of the Committee on Incorporating 21st Century Science into Risk-Based Evaluations** This committee was established to provide	At the April 2015 meeting, ICCVAM member Suzanne Fitzpatrick, Ph.D., presented the talk "Risk-Based Decision-Making at the FDA." At the June 2015 meeting, Casey presented on "Validation

		recommendations on integrating new scientific approaches into risk-based evaluations.	Principles for Tox21."
April 21, 2015 Sacramento, California	California Environmental Protection Agency Department of Pesticide Regulation and Physicians Committee for Responsible Medicine	**Symposium on In Vitro Skin Sensitization** This symposium focused on advances in skin sensitization determination with in vitro and in silico models.	Kleinstreuer gave the presentation "Integrated Computational Approaches to the Assessment of Skin Sensitization Potential of Chemicals."
June 23-26, 2015 Jeju City, South Korea	Asian Society of Toxicology	**ASIATOX 2015 International Congress** This is a triennial international congress held to facilitate and encourage scientific exchange and leadership.	Casey gave the presentation "Advances in the Development and Validation of Test Methods in the United States."

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NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

BIENNIAL PROGRESS REPORT 2014-2015

Interagency Coordinating Committee on the Validation of Alternative Methods

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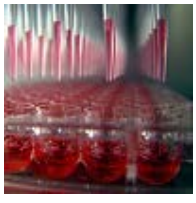
About NICEATM and ICCVAM

The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3) established the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to "establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid safety testing methods that protect human and animal health and the environment while reducing, refining, and replacing animal tests and ensuring human safety and product effectiveness." ICCVAM is supported by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

ICCVAM Establishment and Purpose

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



ICCVAM Duties and Activities

The ICCVAM Authorization Act directs ICCVAM to carry out specific duties relevant to evaluation and promotion of new test methods. This page lists those duties and how key activities in 2014 and 2015 align with those duties.

How NICEATM Supports ICCVAM

NICEATM is an office within the National Institute of Environmental Health Sciences' Division of the National Toxicology Program. NICEATM provides technical and scientific support for ICCVAM and ICCVAM working group activities, peer review panels, expert panels, workshops, and validation efforts.

ICCVAM Advisory Committee

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) advises the Director of the National Institute of Environmental Health Sciences, NICEATM, and ICCVAM about NICEATM and ICCVAM activities.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

ICCVAM Establishment and Purpose

U.S. regulatory agencies are charged to protect human and animal health and the environment. To do this, agencies must determine the hazards presented by substances such as pesticides, consumer products, and workplace chemicals. Testing these substances provides information about possible hazards and enables informed decisions about responsible use, storage, and disposal.

Many currently accepted test methods use laboratory animals. Alternative test methods are methods that *replace* animal use with non-animal test systems or lower species, *reduce* the number of animals required for a specific test procedure, or *refine* animal use to enhance animal well-being and lessen or avoid pain and distress. Collectively, the principles of replacement, reduction, or refinement of animal use for scientific research or product safety testing are referred to as the 3Rs.

The ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3) directs the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to "establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid safety testing methods that protect human and animal health and the environment while reducing, refining, and replacing animal tests and ensuring human safety and product effectiveness."

The ICCVAM Authorization Act states that the purposes of ICCVAM are to:

- Increase the efficiency and effectiveness of federal agency test

ICCVAM Member Agencies

- Agency for Toxic Substances and Disease Registry (ATSDR)
- National Cancer Institute (NCI)
- National Institute for Occupational Safety and Health (NIOSH)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institutes of Health (NIH)
- National Library of Medicine (NLM)
- Occupational Safety and Health Administration (OSHA)
- U.S. Consumer Product Safety Commission (CPSC)
- U.S. Department of Agriculture (USDA)
- U.S. Department of Defense (DOD)
- U.S. Department of Energy (DOE)

method review
- Eliminate unnecessary duplicative efforts and share experiences between federal regulatory agencies
- Optimize utilization of scientific expertise outside the federal government
- Ensure that new and revised test methods are validated to meet the needs of federal agencies
- Reduce, refine, and replace the use of animals in testing, where feasible

ICCVAM is a permanent interagency committee of the National Institute of Environmental Health Sciences (NIEHS) under the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Methods (NICEATM).

- U.S. Department of the Interior (DOI)
- U.S. Department of Transportation (DOT)
- U.S. Environmental Protection Agency (EPA)
- U.S. Food and Drug Administration (FDA)

next article - "ICCVAM Duties and Activities ..."

ICCVAM Duties and Activities

The ICCVAM Authorization Act directs ICCVAM to carry out the following duties:

- Coordinate the technical review and evaluation of new, revised, or alternative test methods
- Foster interagency and international harmonization of test protocols that encourage replacing, reducing, and refining animal test methods
- Assist with and provide guidance on validation criteria and processes
- Promote the acceptance of scientifically valid test methods
- Promote awareness of accepted test methods
- Submit ICCVAM test method recommendations to appropriate U.S. federal agencies
- Consider requests from the public to review and evaluate new, revised, or alternative test methods that have evidence of scientific validity
- Make ICCVAM's final test recommendations available to the public
- Prepare reports on ICCVAM progress and accomplishments under the Act and make them available to the public

Since its establishment, ICCVAM and ICCVAM member agencies have contributed to the development and regulatory acceptance of a number of alternative methods that address a variety of regulatory applications. These methods are listed on the NTP website.

The table below notes how selected 2014-2015 ICCVAM and ICCVAM agency activities align with the ICCVAM duties as outlined in the ICCVAM Authorization Act.

ICCVAM Duty	Activity
	• Provided oversight and direction for validation study of the

Review and evaluate new, revised, or alternative test methods	OptiSafe test method for ocular irritation • Developed a computational approach that integrates several types of data to predict human skin sensitization hazard without using animals • Evaluated an integrated testing strategy for identifying potential skin sensitizers without using animals • Explored whether data from acute oral toxicity tests could be used to assign EPA dermal hazard classifications, thereby eliminating the need for separate acute dermal toxicity tests
Facilitate appropriate interagency and international harmonization of test protocols that encourage reducing, refining, and replacing animal test methods	• Participated on management teams for validation studies conducted by Japan and the European Union • Organized two workshops to evaluate ongoing studies of alternatives to the murine histamine sensitization test for safety testing of acellular pertussis vaccines • Presented a webinar on in vitro to in vivo extrapolation to encourage research and collaboration in this area
Facilitate and provide guidance on validation criteria and processes	• Defined lists of reference chemicals and associated potencies that can be used for future validation of novel androgen receptor and estrogen receptor assays • Published "Guidelines for Validation of In Vitro Potency Assays"
Promote the acceptance of scientifically valid test methods	• Published "Process for Establishing and Implementing Alternative Approaches to Traditional In Vivo Acute Toxicity Studies" • Adopted high throughput assays and computational models for detecting and measuring estrogen receptor bioactivity as an alternative to three Tier 1 tests used in the Endocrine Disruptor Screening Program to assess estrogen receptor activity • Published Final Rule to update the definition of "strong sensitizer" and clarify the acceptability of in vitro test data for characterization of substances as strong sensitizers • Participated in and supported a series of workshops that

	produced recommendations on use of an in vitro test with potential to replace animal use for pertussis vaccine testing
Promote awareness of accepted test methods	• Presented webinar to EPA employees on Validation and Utilization of Alternative Test Methods
Prepare reports on ICCVAM progress and accomplishments under the Act and make them available to the public	• Published ICCVAM Biennial Progress Report 2012-2013 • Provided updates at 2014 and 2015 ICCVAM public forum meetings

"ICCVAM Establishment and Purpose ..." - previous article

next article - "How NICEATM Supports ICCVAM ..."

How NICEATM Supports ICCVAM

NICEATM is an office within the National Institute of Environmental Health Sciences' Division of the National Toxicology Program (DNTP). NICEATM provides technical and scientific support for ICCVAM and ICCVAM working group activities, peer review panels, expert panels, workshops, and validation efforts.

In addition to providing support for ICCVAM, NICEATM:

- Supports DNTP activities, especially those contributing to the U.S. government's interagency Tox21 initiative
- Conducts analyses and evaluations and coordinates independent validation studies on novel and high-priority alternative testing approaches
- Provides information to test method developers, regulators, and regulated industry through its website and workshops on topics of interest

About Tox21

Most traditional toxicity testing methods involve treating a laboratory animal with a test substance and observing adverse effects. This approach is expensive and time-consuming and raises concerns about the ethical use of animals and interspecies variability.

Tox21 is a collaboration among four U.S. federal agencies aimed at developing more efficient approaches to predict how chemicals may affect human health. Tox21 studies use assays that measure the effects of test chemicals on rodent and human cells, chemical interactions, and lower organisms. These assays are run at higher throughput and lower cost than traditional tests; in some cases, many thousands of chemicals can be tested in a few days. The goal of Tox21 is to use data from these

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assays to prioritize substances for further evaluation, inform understanding of mechanisms of action, and/or develop improved predictive models for toxicity.

Test approaches developed and data collected via this initiative may enable agencies to reduce reliance on animal data for assessing chemical safety. For example, in 2015, the U.S. Environmental Protection Agency (EPA) announced a plan to adopt high throughput screening assays and computational models for detecting and measuring estrogen receptor bioactivity as an alternative for three Tier 1 tests currently used in its Endocrine Disruptor Screening Program to assess estrogen receptor activity. This decision was based on a NICEATM and EPA evaluation that included Tox21 data.

The four agencies participating in the Tox21 collaboration are ICCVAM members:

- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- National Institute of Environmental Health Sciences
- National Institutes of Health (National Center for Advancing Translational Sciences)

"ICCVAM Duties and Activities ..." - previous article

next article - "ICCVAM Advisory Committee ..."

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ICCVAM Advisory Committee

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) was established in 2002 in accordance with the ICCVAM Authorization Act. SACATM advises the Director of the National Institute of Environmental Health Sciences, NICEATM, and ICCVAM about NICEATM and ICCVAM activities.

The ICCVAM Authorization Act states that SACATM must include:

- At least one member from each of the following stakeholder groups:
  - — The personal care, pharmaceutical, industrial chemicals, or agriculture industry
  - — Any other industry regulated by one of the ICCVAM agencies
  - — A national animal protection organization
- Additional representatives selected from among the following:
  - — Academic institutions
  - — State government agencies
  - — An international regulatory body
  - — Any corporation developing or marketing new or revised or alternative test methods, including contract laboratories

SACATM Meetings

SACATM, which is directed by its charter to meet at least once each fiscal year, met in September 2014 and September 2015.

- Summaries of 2014 and 2015 SACATM meetings
- Roster of SACATM members during 2014 and 2015

"How NICEATM Supports ICCVAM ..." - previous article

NICEATM with a copy for our records. Send comments or suggestions to NICEATM.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Reference Pages

Agency Representatives in 2014 and 2015

The individuals listed on this page served as designated representatives from ICCVAM member agencies in 2014 and 2015.

NICEATM and ICCVAM Publications, 2014-2015

This page lists publications issued in 2014 and 2015 that describe NICEATM and ICCVAM activities.

Roster of SACATM Members 2014-2015

This page lists all members of the Scientific Advisory Committee on Alternative Toxicological Methods during 2014 and 2015 and indicates ending dates of appointments.

Definitions of Key Terms

This page lists definitions of key terms used throughout the report. Definitions of terms can also be viewed by hovering your mouse over terms that appear in text.

Acronyms and Abbreviations

This page lists acronyms and abbreviations used throughout the ICCVAM Biennial Report.

NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Agency Representatives in 2014 and 2015

Show 10 entries Select Columns Search: Search Table

Agency (Office)	Representative
Agency for Toxic Substances and Disease Registry	Moiz Mumtaz, Ph.D.
Agency for Toxic Substances and Disease Registry	Edward Murray, Ph.D.
Consumer Product Safety Commission	Joanna Matheson, Ph.D.
Consumer Product Safety Commission	Kristina Hatlelid, Ph.D.
Department of Agriculture	Carol Clarke, D.V.M., DACLAM
Department of Agriculture	Kristina Adams, M.S.
Department of Agriculture	Donna Malloy, D.V.M., DACLAM
Department of Agriculture	Tim Allen
Department of Defense	Patrick Mason, Ph.D., SES
Department of Defense	Dawn Fitzhugh, VMD, MPH

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next article - "NICEATM and ICCVAM Publications, ..."

Warren Casey

Elizabeth Maull

Editor: Catherine Sprankle

NICEATM and ICCVAM Publications, 2014-2015

NICEATM and ICCVAM Reports

ICCVAM. 2014. Biennial Progress Report 2012-2013: Interagency Coordinating Committee on the Validation of Alternative Methods. Research Triangle Park, NC:National Institute of Environmental Health Sciences.

Federal Register Notices

Manuscripts

Abstracts

Articles in the National Institute of Environmental Health Sciences *Environmental Factor* Newsletter

"Agency Representatives in 2014 ..." - previous article

next article - "Roster of SACATM Members ..."

Maull | Report Editor: Catherine Sprankle

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Sprankle C. April 2014. Collaboration, focus, and innovation keys to replacing animal use.

Sprankle C. June 2014. Small fish may offer big opportunities for future toxicity testing.

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NICEATM Director: Warren Casey | NICEATM Program Administrator: Elizabeth Maull | Report Editor: Catherine Sprankle

Roster of SACATM Members 2014-2015

Name	Title	Company	Appointment End Year
Lauren E. Black, Ph.D.	Senior Scientific Advisor, Navigators Services	Charles River Laboratories, Reno, NV	2016
Tracie E. Bunton, D.V.M., Ph.D.	President and Founder	Eicarte LLC, Gettysburg, PA	2015
Joy Cavagnaro, Ph.D., DABT, RAC, ATS, RAPS	President and Founder	Access BIO, LC, Boyce, VA	2014
Joan M. Chapdelaine, Ph.D.	Senior Immunologist	Calvert Laboratories, Inc., Tunkhannock, PA	2015
Mark G. Evans, D.V.M., Ph.D., ACVP	Research Fellow, Drug Safety Research and Development	Pfizer Global Research and Development La Jolla Laboratories, San Diego, CA	2015
William P. Janzen	Professor, Eshelman School of Pharmacy	University of North Carolina at Chapel Hill, Chapel Hill, NC	2017
Michael D. Kastello, D.V.M., Ph.D.	Vice President and Global Head, Animal Research and Welfare	Sanofi, Bridgewater, NJ	2016
Safdar A. Khan, D.V.M., M.S., Ph.D., DABVT	Senior Toxicologist and Senior Director of Toxicology Research	ASPCA Animal Poison Control Center, Urbana, IL	2016
Ricardo Ochoa, D.V.M., Ph.D., ACVP	President and Principal	Pre-Clinical Safety, Inc., Niantic, CT	2014
Catherine E. Willett, Ph.D.	Director, Regulatory Toxicology, Risk Assessment, and Alternatives	The Humane Society of the United States, Gaithersburg, MD	2017
Daniel M. Wilson, Ph.D., DABT	Mammalian Toxicology Consultant	Toxicology and Environmental Research and Consulting, The Dow Chemical Company	2014

Wei Xu, Ph.D.	Associate Professor, Department of Oncology	McArdle Laboratory for Cancer Research, University of Wisconsin at Madison Madison, WI	2017

"NICEATM and ICCVAM Publications, ..." - previous article

next article - "Definitions of Key Terms ..."

Definitions of Key Terms

3Rs: the principles of replacement, reduction, or refinement of animal use for scientific research or product safety testing

Accuracy: the closeness of agreement between a test method result and an accepted reference value, or the test method's proportion of correct outcomes

Acellular pertussis vaccines: vaccines that contain Bordatella pertussis proteins rather than whole bacterial cells

Acute systemic toxicity: the immediate or near-immediate effect of a toxic substance after it is absorbed and distributed throughout the body. Different acute systemic toxicities are distinguished by the route of exposure: by ingestion (oral), through the skin (dermal), or by inhalation.

Adverse outcome pathway (AOP): a conceptual framework constructed from existing knowledge that relates exposure of a type of toxic substance to subsequent steps that result in illness or injury

Agonist: a substance that increases activity of the target (estrogen or androgen) receptor

Agrochemical: a chemical product used in agriculture

Algorithm: a set of steps that are followed in order to complete a computational process

Allergen: a substance that can cause an allergic reaction

Allergic contact dermatitis (ACD): an allergic reaction that results from repeated direct skin contact with a skin sensitizer. Clinical signs of ACD include redness, swelling, blistering, and itching.

Alternative methods: testing methods that replace, reduce, or refine animal use

Androgen: a class of hormones, produced largely by the testes, that serve as the primary male hormones

Androgen receptor (AR): a protein molecule to which an androgen or androgen-like substance can attach. This interaction produces a chemical signal or triggers a cellular response.

Antagonist: a substance that decreases activity of the target (estrogen or androgen) receptor

Anticoagulant rodenticides: chemicals that inhibit blood clotting that are sold for the purpose of killing rodents

Antimicrobial: capable of destroying or inhibiting the growth of bacteria, fungi, and other microorganisms

Bayesian network: a machine-learning approach used to explore probabilistic relationships among variables of interest

Bioavailability: potential for chemical absorption and distribution throughout the body and into cells, or the extent of chemical accessibility at a physiologically active site

Biocide: in European legislation, a chemical substance or microorganism intended to destroy, deter, render harmless, or exert a controlling effect on any harmful organism by chemical or biological means (a similar but subtly different definition is used by the EPA)

Biomarker: a biological molecule found in blood, other body fluid, or tissues that can be measured and that may provide a sign of toxicity or disease

Biotransformation: the process in a living system of converting a substance to a different substance

Corneal epithelial cells: structural cells from the cornea, the transparent front part of the eye

Cryopreserved cells: cells preserved by cooling to subfreezing temperatures while avoiding damage caused by formation of ice; cryopreservation can be used to preserve cells extracted from tissues for later use

Cytochrome p450 enzymes: a group of enzymes that alter the structure of drugs and other molecules

Cytotoxic: the ability of a substance to kill or harm cells

Developmental toxicity: effects observed in offspring that occur as a result of chemical exposures of the pregnant mother. Developmental toxicity effects may be apparent at birth or emerge later in the offspring's life.

Dosimetry: calculation of dose level or exposure concentration

Ecotoxicity testing: refers both to the assessment of chemical effects on fish, birds, or other wild

organisms and testing of soil, sediment, or effluents for the presence of toxic compounds

Endocrine disruptor: a natural or man-made substance that may interfere with the endocrine system and produce adverse health effects

Estrogen: a class of hormones, produced largely by the ovaries, that serve as the primary female hormones

Estrogen receptor (ER): a protein molecule to which an estrogen or estrogen-like substance can attach. This interaction produces a chemical signal or triggers a cellular response.

Ex vivo: refers to an assay using tissue that has been removed from a multicellular organism and conducted while the tissue is still viable

Formulation: a mixture of chemicals prepared according to a specific procedure to ensure a desired effect when used, improve handling properties, or achieve other desired product goals

Harmonization: the act of making systems or laws similar among different companies, countries, etc., so the organizations using those systems or laws can operate more easily within the different venues

Hazard classification: assignment of a substance to a category according to results of toxicity testing, most often for labeling purposes

High throughput screening (HTS): a testing approach that uses robotics, liquid-handling devices, detectors, and associated software to quickly conduct a large number of chemical or biochemical tests

Immunotoxicity: an adverse effect caused by a substance (an “immunotoxicant”) that disrupts the normal function of the immune system

In chemico: refers to a test method that measures the interaction of a test chemical with protein or DNA molecules rather than living cells

In silico: refers to analyses that are carried out on a computer or via computer simulation

In vitro: refers to assays that are carried out in an artificial system such as a test tube or assay plate using small single-celled or multicellular organisms, cultured cells, or cellular components

In vitro to in vivo extrapolation (IVIVE): an analysis conducted to relate the test chemical concentration causing a response in an in vitro system to concentrations that result in human or animal (“in vivo”) illness or injury at the target tissue

In vivo: refers to assays carried out using multicellular organisms, typically rodents or other mammals

Integrated approaches to testing and assessment (IATA): an approach that considers all available

relevant information about a substance in a weight-of-evidence assessment to inform a regulatory decision regarding hazard or risk or indicate that specific additional tests are needed

Integrated testing strategy: a type of IATA consisting of a fixed data interpretation procedure combining data from a specific set of sources in a parallel, structured, and reproducible manner

LD50: in traditional animal tests, the dose that causes death in 50% of the animals tested; a value used to categorize toxic substances and determine the hazard phrases used on product labels

Machine learning: the study and construction of computer algorithms that, once trained on a set of data, can make predictions or decisions about a different set of data; a Bayesian network is one type of these

Macromolecule: a large molecule, such as a protein, that consists of many smaller molecules linked together

Metabolism: the sum of the processes by which a particular substance is handled in a living organism, such as assimilation and incorporation or detoxification and excretion

Microphysiological organ systems: in vitro models of organs composed of cells and structural materials that are designed to reproduce the function of living organs; also referred to as “organs-on-a-chip”

Murine histamine sensitization test (HIST): a safety test performed using mice to ensure that pertussis toxin in acellular pertussis vaccines has been effectively inactivated

Nanomaterials: a substance made up of particles that measure no more than 100 nanometers in at least one dimension

Ocular corrosive: a substance that causes permanent eye tissue damage

Ocular irritant: a substance that causes temporary eye tissue damage. A severe irritant produces damage persisting 21 days after application or causes serious physical decay of vision.

Pharmacokinetic model: a mathematical model created to describe the process of absorption, distribution, metabolism, and excretion of a chemical through the body. “One-compartment” models treat all organs as a single unit, while “physiologically based” models are usually multi-compartment models with separate compartments corresponding to individual or combined organs and being interconnected by blood flows.

Physicochemical properties: referring to the physical or chemical properties of a substance

Quantitative structure-activity relationship (QSAR) models: classification models that predict the activities of chemicals with unknown properties by relating them to properties of known chemicals

Read-across: a computational technique that uses toxicity data from a known (“source”) chemical to

predict toxicity for another ("target") chemical, usually but not always on the basis of structural similarity

Reduction alternative: a test method that requires fewer animals

Reference data: data from an accepted test method that can be used to assess the performance of a new test method designed to measure an analogous effect

Reference chemical: a chemical that causes a specific well-characterized biological effect and therefore can be used to assess the performance of a test method designed to measure that effect. Reference chemicals should represent the classes of chemicals for which a test method is proposed to be used and cover the range of expected responses.

Refinement alternative: a test method that modifies procedures to enhance animal well-being and lessen or avoid pain and distress in animals

Relevance: the extent to which a test method accurately measures a biological effect of interest in a species of interest

Reliability: the extent to which a test method can be performed reproducibly over time

Replacement alternative: a test method that replaces animals with a non-animal system or one animal species with a phylogenetically lower one

Risk assessment: the process of characterizing the potential risk posed by a chemical, taking into consideration the hazards posed by the chemical, the dose of the chemical needed to cause health problems, and the probability of exposure at that dose

Semipermeable membrane: a barrier that allows some molecules to pass through but not others

Sensitivity: the ability of a new test method to correctly classify a substance as having a particular activity

Skin sensitization: a hypersensitivity that occurs when a susceptible person comes in direct skin contact with an allergen, termed a "skin sensitizer." Once sensitized, a person may have a secondary immune response when exposed to the same allergen again.

Skin sensitization potency: the relative amount of a substance that produces a skin sensitization reaction

Specificity: the ability of a new test method to correctly classify a substance as not having a particular activity

Thrombogenicity: the tendency of a substance (in this case a medical device) to induce blood clot formation

Tier 1 test: in the Endocrine Disruptor Screening Program, a test performed to identify substances that

have the potential to interact with the endocrine system. Chemicals exhibiting the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to Tier 2 testing, which identifies the adverse effect caused by the chemical and establishes a quantitative relationship between the chemical dose and the adverse effect.

Titration (virology): inoculation of an animal with a virus preparation to assess the potency of the preparation for use in vaccine testing

Toxicant: a toxic or poisonous substance

Transcription: the process by which DNA directs production of specific proteins in cells, in this case in response to chemical exposure

Transcriptomics: studies that consider the complete set of RNA transcripts produced in a cell or tissue under specific circumstances, such as in response to chemical treatment

Uterotrophic assay: an assay conducted in female rodents that measures the estrogenic activity of a chemical by assessing the chemical's effect on the weight of the uterus

Vaccination-challenge assay: a potency test requiring the vaccination of animals followed by infection with a virulent pathogen to assess the protection afforded by a specific vaccine

Validation: a process by which the reliability and relevance of a test method are established for its intended application

Viability: ability to live, especially under specific conditions

"Roster of SACATM Members ..." - previous article

next article - "Acronyms and Abbreviations ..."

Acronyms and Abbreviations

3Rs: Principles of replacement, reduction, or refinement of animal use for scientific research or product safety testing

ACD: Allergic contact dermatitis

ADMET CoE: Absorption, Distribution, Metabolism, Elimination, and Toxicology Center of Excellence (U.S. Department of Defense)

AOP: Adverse outcome pathway

AR: Androgen receptor

ASCCT: American Society for Cellular and Computational Toxicology

ATSDR: Agency for Toxic Substances and Disease Registry

CPSC: U.S. Consumer Product Safety Commission

CVB: Center for Veterinary Biologics (U.S. Department of Agriculture)

CYP: Cytochrome P450 enzymes

DNTP: Division of the National Toxicology Program (National Institute of Environmental Health Sciences)

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

DREAM: Dialogue for Reverse Engineering Assessments and Methods

EDQM: European Directorate for the Quality of Medicines and HealthCare

EDSP: Endocrine Disruptor Screening Program (U.S. Environmental Protection Agency)

EPA: U.S. Environmental Protection Agency

EURL ECVAM: European Union Reference Laboratory for Alternatives to Animal Testing

FDA: U.S. Food and Drug Administration

FR: *Federal Register*

HIST: Murine histamine sensitization test

HSDB: Hazardous Substance Data Bank (National Library of Medicine)

HTS: High throughput screening

IATA: Integrated approach to testing and assessment

ICATM: International Cooperation on Alternative Test Methods

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ILS: Integrated Laboratory Systems, Inc.

IVIVE: In vitro to in vivo extrapolation

JaCVAM: Japanese Center for the Validation of Alternative Methods

KoCVAM: Korean Center for the Validation of Alternative Methods

LD50: In traditional acute systemic toxicity tests, the dose that produces lethality in 50% of the animals tested

LLNA: Murine local lymph node assay

NC3Rs: National Centre for the 3Rs (United Kingdom)

NCI: National Cancer Institute (National Institutes of Health)

NCSU: North Carolina State University

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

NIEHS: National Institute of Environmental Health Sciences (National Institutes of Health)

NIOSH: National Institute for Occupational Safety and Health

NIH: National Institutes of Health

NLM: National Library of Medicine (National Institutes of Health)

NTP: National Toxicology Program

OECD: Organisation for Economic Co-operation and Development

OSHA: Occupational Safety and Health Administration

P&G: Procter & Gamble

PISC: PETA International Science Consortium, Ltd.

QSAR: Quantitative structure-activity relationship

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals (European Union legislation)

SACATM: Scientific Advisory Committee on Alternative Toxicological Methods

SEAZIT: Systematic Evaluation of the Application of Zebrafish in Toxicology (National Toxicology Program)

SOT: Society of Toxicology

STE: Short time exposure

Tox21: Collaborative effort among four U.S. federal government agencies to develop more efficient approaches to predict how chemicals may affect human health

ToxCast: Toxicity Forecaster (U.S. Environmental Protection Agency)

TOXNET: Toxicology Data Network (National Library of Medicine)

U.S.C.: United States Code

USDA: U.S. Department of Agriculture

USGS: U.S. Geological Survey (U.S. Department of the Interior)

XCEL: Ex Vivo Countermeasure Evolution and Licensure Program (U.S. Department of Defense)

"Definitions of Key Terms ..." - previous article

next article - "Abstracts ..."

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