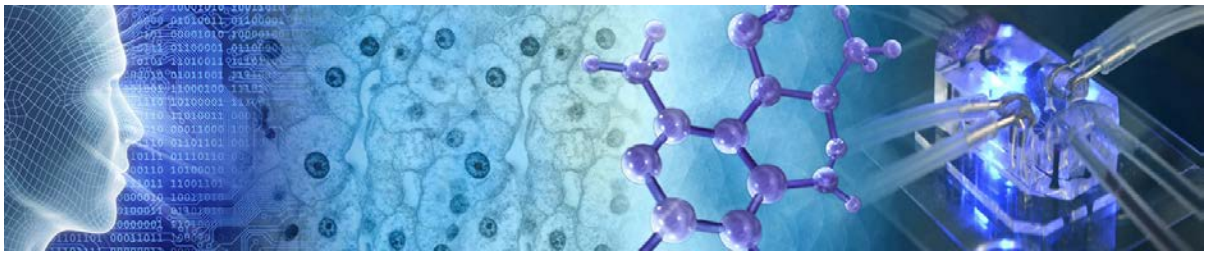
Biennial Progress Report 2016-2017

Interagency Coordinating Committee on the Validation of Alternative Methods



July 2018

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About this Report

ICCVAM facilitates the development, validation, and regulatory acceptance of test methods that replace, reduce, or refine the use of animals in testing.

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 from January 2016 through December 2017.

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

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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 2016 and 2017, 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).

We are very proud of the NICEATM and ICCVAM accomplishments summarized in this report. We particularly applaud the leadership roles taken by NICEATM and ICCVAM during the development of the Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. The Strategic Roadmap establishes a framework to successfully implement testing approaches that will utilize 21st century science to protect and improve public health. The collaborative and transparent approach taken by NICEATM and ICCVAM to develop the Strategic Roadmap effectively sets the stage for the collaborative and transparent approach that will be needed to foster acceptance of these new testing approaches.

The 2016-2017 Biennial Report describes a number of other important activities undertaken by ICCVAM and ICCVAM agencies to advance the ICCVAM mission. NICEATM and ICCVAM worked with stakeholders both within the U.S. and internationally to achieve major progress in advancing technologies that will reduce or replace animal use when identifying substances with the potential to cause allergic contact dermatitis. Advances were also made to reduce or replace animal use for acute systemic toxicity testing and identification of potential endocrine disruptors. NICEATM's Integrated Chemical Environment, launched in 2017, will provide appropriate data and visualization tools needed to support continued progress towards these goals.

We are pleased to note the recognition that these accomplishments have received from ICCVAM's stakeholder communities. NICEATM Deputy Director Nicole Kleinstreuer, Ph.D., was honored in 2016 with the F. Clarke Fraser New Investigator Award from the Teratology Society and the Lush Cosmetics Young Researcher – Americas Prize for her research on mathematical and computational modeling of biological systems. NICEATM and ICCVAM scientists were also recognized by the Society of Toxicology with the Enhancement of Animal Welfare Award. David Allen, Ph.D., of Integrated Laboratory Systems, Inc., received the award in 2017 for his work as principal investigator on the NICEATM support contract. ICCVAM Co-chair Anna Lowit, Ph.D., of the U.S. Environmental Protection Agency (EPA) received the award in 2018, in recognition both of her leadership of ICCVAM and her efforts in the EPA Office of Pesticide Programs to improve risk assessments while reducing animal use in toxicity testing.

Development, acceptance, and implementation of new approach methodologies have become central themes in toxicology, and NICEATM and ICCVAM are playing key roles in these areas. As we reflect on the accomplishments of the past two years, we are also looking forward to continued success in achieving the vision of 21st century toxicology.

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A Message from NICEATM and ICCVAM

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 2016-2017 ICCVAM Biennial Progress Report. This report describes activities of ICCVAM and its 16 member agencies that support the ICCVAM mission of facilitating development, validation, and regulatory acceptance of new testing approaches.

A major activity for ICCVAM during this period was development and publication of the Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. This document, released in January 2018, reflects the contributions of dozens of representatives of ICCVAM member agencies as well as input from ICCVAM stakeholders. We envision that the Strategic Roadmap will expedite the development and use of new approach methodologies that provide information more relevant to human health than existing animal-based methods.

In addition to describing development of the Strategic Roadmap, this Biennial Report summarizes a broad range of activities undertaken during 2016 and 2017 by ICCVAM member agencies to advance alternatives to animal use for chemical safety testing. Some of these activities focus on reducing animal use, such as guidances issued by the U.S. Environmental Protection Agency and U.S. Department of Agriculture that allow waiving of required animal tests under specific circumstances. Other activities have the potential to replace animal use, such as implementation of non-animal approaches developed by ICCVAM agency scientists to identify potential skin sensitizers and endocrine disruptors.

ICCVAM continues to work with NICEATM on outreach efforts. These activities raise awareness of available alternative methods and foster partnerships with stakeholders to maximize efficiency of development, validation, and implementation of new methods. During 2016 and 2017, ICCVAM convened two Public Forum meetings and participated in two public meetings of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). The Public Forums were each viewed by dozens of 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 enabled the SACATM meetings to focus on substantive strategic and technical discussions to better leverage the expertise of the SACATM members in advancing the ICCVAM mission. NICEATM and ICCVAM also presented webinar series on alternative approaches for inhalation toxicity and improving data analysis for chemical screening assays conducted in zebrafish, as well as two ICCVAM Communities of Practice webinars on current topics in cheminformatics.

For the first time since ICCVAM was established, ICCVAM added a new member agency to the committee. In March 2016, the National Institute of Standards and Technology (NIST) became the 16th ICCVAM member agency, bringing expertise and interest in measurement science and method validation to ICCVAM's activities. The Biennial Report describes several NIST activities, undertaken both independently and in collaboration with other ICCVAM agencies.

We gratefully acknowledge the contributions of the representatives and interagency working group members from the 16 ICCVAM member agencies, particularly those who applied their insight and expertise to development of the Strategic Roadmap. Special thanks and recognition are due to Abigail Jacobs, Ph.D., who retired from the U.S. Food and Drug Administration in 2017 after many years of service to ICCVAM, including nearly five years serving as the Committee's co-chair. 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.

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Key NICEATM and ICCVAM Accomplishments and Impact

During 2017, ICCVAM coordinated the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. The U.S. Strategic Roadmap was developed with participation from all ICCVAM member agencies and multiple interagency workgroups, with input from a broad range of stakeholder groups.

Other key accomplishments of ICCVAM and ICCVAM member agencies in support of the ICCVAM mission during 2016 and 2017 include:

- Publication of two guidance documents by the U.S. Environmental Protection Agency (EPA) in 2016. One included a policy statement to waive all acute dermal lethality studies for pesticide formulations. The other described a transparent, stepwise process for evaluating and implementing alternative methods for six-pack studies, which test for acute systemic toxicity by the oral, dermal, and inhalation routes; skin and eye irritation; and skin sensitization.
- Publication of notices permitting removal of back-titration hamsters for potency testing of vaccines containing *Leptospira pomona* and *Leptospira grippotyphosa* by the U.S. Department of Agriculture (USDA), further reducing the number of hamsters required for potency testing of leptospirosis vaccines.
- Publication of the Predictive Toxicology Roadmap for integrating predictive toxicology methods into safety and risk assessments by the U.S. Food and Drug Administration (FDA) in 2017.
- Development of a defined approach that combines data from 11 high-throughput screening (HTS) assays with a computational model to identify chemicals with the potential to interact with the androgen receptor pathway by NICEATM and EPA scientists.
- Development of a defined approach that uses non-animal approaches to predict murine local lymph node assay outcomes and human skin sensitization hazard and potency by NICEATM and ICCVAM scientists.

- Submission of a proposal in 2016 to the Organisation for Economic Co-operation and Development (OECD) by partners in the International Cooperation on Alternative Test Methods, including NICEATM, ICCVAM, EURL ECVAM, and Health Canada, on the development of a performance-based test guideline for defined approaches to skin sensitization testing and assessment. The proposal was approved as part of the OECD workplan in 2017.
- Launch of the Integrated Chemical Environment, a publicly accessible online resource developed to provide high-quality curated data and computational workflows to facilitate chemical safety assessment by NICEATM.

ICCVAM Agency Activities 2016-2017

Acute Systemic Toxicity

Acute systemic toxicity tests are commonly used to evaluate the potential hazards of chemicals, medical products, and other substances via three routes of exposure: ingested (oral toxicity tests), absorbed through the skin (dermal toxicity tests), or inhaled (inhalation toxicity tests). Testing substances to characterize their toxicity provides data that can be used to develop product protective packaging and warning labels, personal protective equipment requirements, and environmental release guidelines.

Acute systemic toxicity tests provide an LD50 or LC50 value, representing respectively the dose (for oral and dermal tests) or concentration (for inhalation tests) that would be expected to produce lethality in 50 percent of the animals tested. The LD50 or LC50 value is used to assign substances to toxicity categories that determine language for product labels to indicate precautions to be taken while handling. (LD50 or LC50 may not be used in the assessment of acute systemic toxicity for some medical products, such as medical devices.)

NICEATM and ICCVAM agencies are working to develop, validate, and implement approaches with the potential to reduce and replace animal use for acute toxicity testing.

DOD: High-content Screening to Predict Hepatotoxicity

High-content screening uses fluorescent tagging and automated imaging to assess changes in the structure and composition of individual cells in a high-throughput manner. The U.S. Army is using high-content screening to screen potential medical countermeasure drugs based on favorable liver toxicity profiles. This two-tiered screening approach uses immortalized HepG2 liver cells and human primary hepatocytes to assess potential drug-induced toxicities. Endpoints assessed in this approach include nuclear changes, mitochondrial inhibition, cell cycle arrest, steatosis, p53 activation, oxidative stress, phospholipidosis, and cell death. Assays used were extensively validated during 2016 and 2017, and now are available for predictive toxicity assessments of potential therapeutics of interest to the U.S. Department of Defense (DOD). Reports of these assessments include graphed results of all measured parameters, a table of curve fit parameters, a human hepatotoxicity risk assessment, and recommendations for follow-up studies. This approach is

being expanded to assess cardiotoxicity endpoints such as cardiomyocyte hypertrophy and mitochondrial dysfunction.

DOD: Multitier Approach for Toxicity Screening

The U.S. Air Force (USAF) needs the ability to rapidly and systematically evaluate toxicity and physiological changes associated with aerospace environments. This task requires versatile *in vitro* model systems that allow rapid, quantitative, systematic testing while mimicking the *in vivo* tissue microenvironment. To address this need, the USAF established a multitier evaluation approach that incorporated rapid *in vitro* screening, mechanistic *in vitro* studies, limited *in vivo* studies, and *in silico* approaches. Human-derived, three-dimensional co-cultures representing the lung, skin, brain, liver, and kidney were developed that include immune cell function. A system specific for respiratory toxicants includes cell models representing the nasal, bronchial, and alveolar regions of the respiratory pathway. Preliminary studies evaluated aerospace toxicology targets, including energetic nanomaterials and heavy metals. Specifically, studies using chromium and cadmium demonstrated region-specific toxicity in the respiratory screen, with soluble metals being more toxic in the nasal region and insoluble metals displaying greater toxicity in the alveolar region. Stem cells are being developed as additional *in vitro* models to improve predictive capability. The benefits of this approach are lower cost for evaluating physiological and toxicological changes, more rapid screening, use of fewer research animals, and the capability to assess a larger number of experimental conditions with greater predictive power, all of which provide greater protection for personnel working in different operational environments.

EPA: Guidance on Implementing Alternatives to Traditional In Vivo Acute Toxicity Studies for FIFRA

In March 2016, EPA published Process for Establishing & Implementing Alternative Approaches to Traditional In Vivo Acute Toxicity Studies for FIFRA Regulatory Use. This guidance document described a transparent, stepwise process for evaluating and implementing alternative methods for the six-pack studies, which test for acute oral, dermal, and inhalation toxicity; skin and eye irritation; and skin sensitization. The document included discussion of three major phases of the evaluation and implementation process, as well as the implications for reporting information required by the Federal Insecticide, Fungicide and

Rodenticide Act (FIFRA). Establishment of this process and the clear articulation of the related reporting requirements addressed challenges associated with adopting alternative methods.

EPA: Guidance on Waiving Acute Dermal Toxicity Tests for Pesticide Formulations

In November 2016, EPA published Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations and Supporting Retrospective Analysis. The new guidance expanded the potential for data waivers for acute dermal studies and included a policy statement to waive all acute dermal lethality studies for formulated pesticide products. EPA expects this waiver guidance to reduce the use of laboratory animals, potentially up to 2,500 or more each year.

EPA: Pilot Program to Evaluate the GHS Mixtures Equation

In December 2016, EPA launched a voluntary pilot program to evaluate the usefulness and acceptability of a mathematical tool that estimates the toxicological classification of a chemical mixture. The mathematical tool, known as the GHS Mixtures Equation, is used in the United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Use of the GHS Mixtures Equation can reduce animal use for oral and inhalation toxicity studies of pesticide formulations. This program supports the EPA goal of reducing animal testing by adopting better testing methods, as described in the March 2016 Letter to Stakeholders issued by former Office of Pesticide Programs Director Jack Housenger.

EPA requested submission of acute oral and acute inhalation toxicity study data paired with mathematical calculations (GHS Mixtures Equation data) to support the evaluation of pesticide product formulations. The request was accompanied by guidance on how pesticide companies can submit data for the program. At the end of 2017, EPA was still accepting data submissions, with plans to conduct an analysis in 2018.

EPA/NIEHS: Evaluation of Variability in LD50 Data

NICEATM and EPA scientists examined a data set of over 21,000 *in vivo* LD50 values obtained from multiple curated databases to assess data variability in animal studies. Alternative models developed for estimating acute systemic toxicity are generally evaluated using LD50 values from animal studies that can produce variable results, even when

conducted according to accepted test guidelines. Such variability can make assessment of alternative models extremely challenging when these data are used as reference values. Within the LD50 data set examined by NICEATM and EPA, a degree of variability was observed that had the potential to confound hazard categorization. Specifically, LD50 values from 59 chemicals fell into at least three different GHS oral acute toxicity labeling categories, and values from 49 chemicals fell into at least three EPA hazard categories. These findings underscore the importance of considering an appropriate margin of uncertainty when using *in vivo* oral acute toxicity data to assess the performance of alternative methods.

This data set will be made available in 2018 through the NICEATM Integrated Chemical Environment and provide a reference data set to ensure that appropriately representative LD50 data are routinely used for the development and validation of alternative models. The analysis of the full data set will be presented at the 2018 annual meeting of the Society of Toxicology (Karmaus et al.), and a journal article describing the analysis is in preparation.

NIEHS: Use of HTS Data and QSAR Models to Predict Acute Systemic Toxicity

Although cytotoxicity assay data cannot currently be used to replace animal tests for predicting acute hazard classes, two *in vitro* cytotoxicity assays have been validated to estimate starting doses for acute oral toxicity tests in animals. To more broadly investigate the utility of cytotoxicity and other data from *in vitro* assays to predict acute lethality, NICEATM used HTS data from the ToxCast and Tox21 programs to predict LD50 values and binary toxicity categories (toxic vs. nontoxic). To further investigate the correlation of *in vitro* to *in vivo* results, reverse toxicokinetics was used to estimate equivalent administered doses from *in vitro* effective concentrations. These analyses confirmed that no single *in vitro* assay can currently predict acute systemic toxicity in rodents. The analyses were presented (Strickland et al.) at the 2017 World Congress on Alternatives and Animal Use in the Life Sciences.

To follow up on these results, NICEATM conducted an analysis using the random forest machine learning method and data from ToxCast and Tox21 to determine whether a specific group of high-throughput assays could be identified that would be informative in predicting oral LD50 values. Preliminary results using a data set including about 1,700 chemicals and about 200 ToxCast and Tox21 assays suggested that the approach might be able to

distinguish toxic from nontoxic chemicals, especially if the nontoxic chemicals were conservatively defined as those having LD50 values greater than 5,000 milligrams per kilogram of body weight. Ongoing work will apply this approach to a larger data set, explore the use of other machine learning methods, and revise the approach to consider cheminformatics and mechanistic information.

Biologics and Vaccine Testing

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 FDA and 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 exploring approaches to reduce or eliminate the need for animal testing for biologics.

USDA: Exemptions to Reduce Live Animal Use in Leptospira Vaccine Potency Testing

Leptospirosis is a transmissible bacterial disease of animals and humans caused by infection with any of the pathogenic members of the genus *Leptospira*. The organism is shed in the urine and milk of infected animals; infection can cause liver or kidney damage that can be fatal. Disease transmission to man and animals is reduced by the vaccination of cattle, swine, and dogs. Testing to determine vaccine potency is required by law.

In April 2017, the USDA Animal and Plant Health Inspection Service Center for Veterinary Biologics (CVB) issued CVB Notice 17-06, Option to Remove Back-titration Hamsters from In Vivo Potency Tests for *Leptospira* Serogroups *Pomona* and *Grippotyphosa*. This exemption to the test codified in 9 CFR 113 §101-104 can reduce animal use up to 50 percent for testing vaccines for these *Leptospira* serogroups. CVB Notice 17-06, along with the 2015 CVB Notice 15-13, Option to Remove Back-titration Hamsters from In Vivo Potency Tests for *Leptospira* Serogroups *Canicola* and *Icterohaemorrhagiae* are available on the USDA website.

CVB Notice 17-06 is the latest action in a continuing effort by USDA to reduce the number of hamsters required for potency testing of leptospirosis vaccines. In addition, CVB has started to ship cryopreserved leptospirosis challenge cultures to manufacturers upon request. Cryopreserved cultures reduce the number of live animal passages to maintain the virulence of the challenge organisms.

Computational Toxicology

Computational toxicology uses mathematics, informatics, and computer models to better understand toxicity mechanisms and predict toxic effects. ICCVAM agencies are exploring how these approaches could reduce and replace animal use for chemical safety testing.

DOD: Computational Rapid Identification Scientific Threat Analysis

The goal of the Defense Threat Reduction Agency's Computational Rapid Identification Scientific Threat AnaLysis (CRISTAL) effort is to develop a computational approach to predict key attributes (such as physicochemical properties, environmental fate, and toxicity) of emergent threat agents. This approach will use a three-phase process to evaluate chemical properties, enabling a more rapid understanding of the relative threat of chemical substances than is possible using traditional laboratory testing. In the first phase, quantitative models will be used to predict physicochemical properties, which are then confirmed in limited laboratory evaluations. Second, chemical compounds with physicochemical properties that are consistent with a potential use as a threat agent will advance to the next stage, using algorithms to estimate a chemical's environmental behavior, as well as its absorption, disposition, metabolism, and excretion profile. Third, computational estimates can then be confirmed and refined through laboratory experiments and limited animal validation studies.

NIEHS: Integrated Chemical Environment

Successful computational toxicology projects depend on high-quality data that are freely available and formatted for use in computational workflows. The NICEATM Integrated Chemical Environment (ICE) was developed to address the needs frequently expressed by NICEATM stakeholders. Launched in March 2017, ICE provides high-quality, curated data from NICEATM, its partners, and other resources, as well as tools to facilitate chemical safety assessment.

As of the end of 2017, ICE included data from animal and non-animal tests that assessed regulatory endpoints such as acute oral toxicity, skin and eye irritation, skin sensitization, and endocrine activity. ICE also includes curated high-throughput screening data from Tox21 and physicochemical property data on chemicals, including solubility, melting point, and molecular weight. Data on EPA formulations allow users to compare labeling categories from EPA six-pack studies with the performance of the formulation's active ingredients in non-animal methods. Downloadable workflows enable predictions of physicochemical properties, skin sensitization potency, and adverse outcome pathway mapping. ICE is open to all users with no registration needed.

Updates to ICE in 2018 will expand the *in silico* prediction models and computational workflows offered to include *in vitro* to *in vivo* extrapolation and characterization of chemicals from the ICE website, as well as through downloadable workflows. Other planned updates include the implementation of application programming interfaces to support availability and use of ICE data in computing environments outside of ICE. As part of the NIEHS mission to make data readily available, data in ICE are accessible through the NTP Chemical Effects in Biological Systems (CEBS) database, which will support use of ICE data in combination with other NIEHS data resources. Work is also ongoing to improve availability of ICE data to all NIH data resources.

NIEHS/EPA: Computational Tools for Physicochemical Properties Prediction

Physicochemical properties of chemicals are used as inputs for computational models that can predict a chemical's potential toxicity, environmental fate, and exposure potential. However, experimental physicochemical property data are not available for many chemicals. NICEATM and EPA scientists developed computational models to rapidly estimate six physicochemical properties: octanol-water partition coefficient, water solubility, boiling point, melting point, vapor pressure, and bioconcentration factor. The performance of the new models was shown to be generally superior to existing resources. The computational models were described in a 2017 publication and are available via the NICEATM Integrated Chemical Environment and the EPA Chemistry Dashboard.

NIEHS/EPA: Computational Models for In Vitro to In Vivo Extrapolation

One key issue encountered with high-throughput *in vitro* testing methods is how to accurately relate chemical concentrations that induce *in vitro* responses to *in vivo* exposure concentrations that result in human or animal illness or injury. This relationship is established through *in vitro* to *in vivo* extrapolation (IVIVE), the topic of a 2016 workshop organized by NICEATM and the EPA National Center for Computational Toxicology. The workshop report was published in December 2017.

Computational toxicologists at NICEATM and collaborators in other branches of NTP and the National Center for Computational Toxicology are developing IVIVE analysis methods. Current work is focused on understanding the impact of various parameters, such as using free plasma concentration as a surrogate for the total plasma concentration and comparing multiple modeling approaches. Application of these IVIVE approaches to predict the potential of chemicals to cause developmental toxicity and interact with the endocrine system was described in presentations by Chang et al. at the 2017 Society of Toxicology annual meeting, 10th World Congress on Alternatives and Animal Use in the Life Sciences, and 2017 annual meeting of the American Society for Cellular and Computational Toxicology. A workflow for conducting these analyses is planned for a future release of the Integrated Chemical Environment.

Developmental and Reproductive 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.

NIEHS: Systematic Evaluation of the Application of Zebrafish in Toxicology

The small size and rapid development of the zebrafish make it a useful vertebrate model for assessing potential effects of chemicals on development in a mid-throughput to high-throughput manner. However, broader adoption of zebrafish for toxicological screening is hindered by deficits in several key areas, including consistency of experimental protocol elements; understanding of mechanisms of chemical absorption, distribution, metabolism, and excretion in zebrafish; and consistency of informatic approaches used for classification of outcomes. NTP established the Systematic Evaluation of the Application of Zebrafish in Toxicology (SEAZIT) program, led by NTP and NICEATM scientists, to enable the broader adoption of zebrafish for toxicological screening.

In 2016, SEAZIT team members conducted a series of interviews with researchers considered to be experts in the use of zebrafish in toxicology studies. Some of these researchers, as well as data science experts, participated in an April 2017 meeting that focused specifically on how to improve zebrafish screening data analysis using ontologies. Information gathered during these discussions will be published in (1) a recommendations document that will capture best practices for data production and analysis, and identify needs to advance the application of zebrafish in toxicology, and (2) a journal article incorporating the meeting discussions within the context of a SEAZIT literature review. Findings will also inform design of an interlaboratory study designed to examine the influence of chorion removal and exposure media renewal on toxicity estimates. The study is planned to begin in 2018.

Ecotoxicity Testing

Ecotoxicity testing refers both to the assessment of chemical effects on fish, birds, or other wildlife species 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 U.S. Department of the Interior (DOI) and EPA, require those that manufacture, handle, and discharge 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 and expect strong progress in this area through 2018 and 2019.

DOI: Assessing Anticoagulant Rodenticide Effects in Hawaiian Triggerfish

Anticoagulant rodenticides are used in conservation biology management to control invasive rodents, which can devastate colonies of ground-nesting birds on island refuges. Fish in coral reefs surrounding island refuges may be exposed to anticoagulant rodenticides during the treatment of the islands. However, there has been virtually no investigation into the sensitivity of fish toward anticoagulant rodenticides. DOI scientists use the up-and-down procedure (OECD TG 425; EPA OPPTS 870.1100) to minimize animal use when determining the sensitivity of fish species to anticoagulant rodenticide exposure. A modified version of the up-and-down procedure extends the observation period and adds clinical pathology endpoints (histopathology and blood-clotting time).

In 2016 and 2017, these studies focused on the effect of anticoagulant rodenticides on Hawaiian triggerfish and surrogate species. Data from these studies will be used to associate lethal and sublethal effects with anticoagulant rodenticide exposure and to determine half-lives of these substances in fish tissues. These data will also be used to understand the potential for human exposure from consumption of fish.

DOI: Integrated Screening Process for Potential Fish Toxicants

Fisheries managers use toxicants to control invasive and undesirable fish species. These substances need to be screened for effects on nontarget species.

The U.S. Geological Survey (USGS) developed a screening process to minimize and replace animal testing while developing new chemical control agents for invasive species. The goal is to identify compounds that are potentially toxic to target species while posing minimal risk to native species. The three integrated phases of the screening process include identifying physical and chemical properties of compounds that affect bioavailability in fish; prescreening of a publicly available chemical databank to prioritize candidate compounds; and screening of selected compounds for cytotoxicity using *in vitro* biological assays, ecotoxicity modeling, and fish cell lines. Although *in vivo* testing continues to be utilized in the development of new fish toxicants, the screening process enables minimization of animal testing while developing a new chemical control agent for invasive species.

Ecotoxicity modeling uses a quantitative structure-activity relationship modeling system that determines species-specific responses to chemical exposures using existing toxicity data and chemical properties. These *in silico* assessment methods can be used to prioritize candidate compounds and estimate cytotoxicity, and can predict more than 2,000 endpoints for nearly 200 species. The models will be available in 2018.

Promising novel toxicants identified in the ecotoxicity modeling step are tested using cellular assays to identify which toxicants have the biological activity required. USGS has developed multiple endpoint assays that measure cell viability based on quantitation of adenosine triphosphate. These assays use cell lines from native species including fathead minnow, bluegill sunfish, rainbow trout, lake sturgeon, and paddlefish, as well as invasive species including silver carp and bighead carp. Compounds that demonstrate potent cytotoxic effects are then selected for *in vivo* assays for toxicity screening.

DOI: Use of Fish Embryo Toxicity Test for Prioritizing Testing of Environmental Contaminants

As part of ongoing assessments of wildlife health, DOI is investigating potential cardiovascular effects on fish from pesticides and pharmaceuticals frequently detected in surface waters and fish tissues. USGS conducts high-content screening of compounds to formulate hypotheses and prioritize compounds for further toxicity testing. This approach reduces animal use, test compound needed, and waste by utilizing pre-feeding fish embryos in a microtiter plate format. These assays can provide evidence to justify larger-scale studies to determine actual risk versus perceived risk of contaminants.

The current high-content screening assay is a developmental cardiotoxicity assay that assesses total body length, pericardial area, intersegmental vessel area, circulation, and heart rate after a 72-hour exposure. This array of endpoints allows for a targeted assessment of toxicity. In addition to an LC50 estimate, the assay provides a relatively rapid mode of action information, allowing formation of hypotheses on sublethal impacts of contaminants. Data derived from these studies on acute toxicity and mode of action for pesticides and pharmaceuticals will support a better understanding of potential effects on wildlife species.

Endocrine Disruptor Testing

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 can 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 directed the 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 and began efforts to standardize and validate test methods to include in the program. EPA and other ICCVAM agencies are currently exploring how HTS approaches can identify potential endocrine disruptors without using animals.

DOI: High-Throughput, In Vitro Assays to Identify Endocrine-Active Substances

Receptor-based *in vitro* transactivation assays are effective tools for screening large numbers of samples for endocrine activity. DOI adapted two commonly used human breast luciferase transactivation cell bioassays, the estrogen agonist/antagonist screening VM7Luc4E2 cell bioassay (previously designated BG1Luc4E2) and an androgen glucocorticoid screening assay using the MDA-Kb2 human breast cancer cell line, to 384-well formats for screening of endocrine-active substances. The adaptations include a fast, accurate, and easy measurement of protein amount in each well via the fluorescamine assay, which enhances precision and accuracy of the results and allows identification of cytotoxic agents. Additionally, use of the fluorescamine assay confirmed improved accuracy of luciferase activity in wells along the edge of the plate (the so-called edge effect), thereby increasing usable wells to the entire plate, not just interior wells. Overall, this method increases the utility of these cell bioassays for screening of endocrine active substances.

EPA/NIEHS: Defined Approaches to Identify Endocrine-Active Substances

NICEATM and EPA scientists developed and validated a defined approach that combines data from 18 HTS assays in an integrated testing strategy to identify chemicals with the potential to interact with the estrogen receptor pathway. Use of this integrated testing strategy was accepted by the EPA in 2015 as an alternative to three assays used in the Endocrine Disruptor Screening Program Tier 1 battery, including the rodent uterotrophic assay.

Similarly, NICEATM and EPA scientists developed an integrated testing strategy that combines data from 11 HTS assays with a computational model to identify chemicals with the potential to interact with the androgen receptor pathway. EPA is currently considering whether this approach, described in a 2017 publication, is potentially useful for replacement of existing Endocrine Disruptor Screening Program tests. EPA anticipates further progress during 2018-2019 to develop and adopt new approach methodologies for Endocrine Disruptor Screening Program testing.

EPA/NIEHS: Reference Data for Evaluations of Methods to Identify Endocrine-Active Substances

To support the estrogen receptor testing strategy described above, NICEATM created a comprehensive database of high-quality in vivo testing data from rodent uterotrophic studies. This database is available to support validation of other *in vitro* test methods and computational models of estrogenic activity. Current projects using the database include evaluation of uterotrophic assay study design and variability, and *in vitro* to *in vivo* extrapolation to facilitate direct comparison of data from HTS assays in the EPA ToxCast program to high-quality *in vivo* data. These analyses will provide insights about the reproducibility and variability of uterotrophic data and allow for the evaluation of *in vitro* assay data utility, including HTS data, for predicting *in vivo* responses.

NICEATM, EPA, and OECD are currently compiling a similar reference database on rodent Hershberger studies, which will be described in two journal articles to be submitted for publication in 2018. This database will support validation of high-throughput assays to identify androgen-active chemicals.

NIEHS: Validation Study of CertiChem Test Method to Identify Chemicals with Androgenic Activity

NICEATM is collaborating with the test method developer CertiChem, Inc., to validate an *in vitro* test method that uses MDA-Kb2 cells to measure androgen receptor agonist and antagonist activity. Testing of 67 reference chemicals will be completed in early 2018 to characterize the reliability and relevance of the method, and subsequent testing of 30 consumer products will evaluate the utility of the method for testing chemical formulations. The study is planned to run through the end of 2018.

Ocular and Dermal Irritation Testing

Chemicals and substances such as personal care products, cleaning supplies, and pesticides are tested to determine if they present eye and skin injury hazards and to classify them for appropriate labeling and packaging. Ocular irritation testing assesses the potential for substances to injure eyes, and dermal irritation testing assess the potential for substances to injure skin. Nearly all of this testing has been conducted using rabbit tests; evaluation of alternatives to the rabbit eye test that replace, reduce, or refine animal use is a high priority for NICEATM and ICCVAM.

ICCVAM/NIEHS: Validation Study of the OptiSafe Test Method

OptiSafe is an *in vitro* test method in which a test substance is applied to a semipermeable membrane. Damage to macromolecules in the membrane is measured to assess the test substance's potential to cause eye irritation.

NICEATM reviewed a validation study conducted by the OptiSafe test method developer, Lebrun Labs, and concluded that the OptiSafe method compared favorably to other *in vitro* ocular toxicity testing methods. NICEATM is currently coordinating a validation study of the OptiSafe test method to demonstrate the reliability of the method among Lebrun Labs and two naïve laboratories. Members of the ICCVAM Ocular and Dermal Irritation Workgroup comprise the validation management team for the study, and the study received support from an NIEHS Small Business Innovation Research grant. Testing was completed in late 2017 and data analyses and an associated report will be submitted for publication in 2018.

ICCVAM/NIEHS: Defined Approaches for Eye Irritation Testing of Agrochemical Formulations

NICEATM and the ICCVAM Ocular and Dermal Irritation Workgroup are collaborating with CropLife America to develop defined approaches for assessing eye irritation potential of agrochemical formulations. CropLife America provided *in vivo* eye irritation test data for over 200 products, along with data from the same substances from one or more *in vitro* assays. NICEATM evaluated the available data and determined that some of the assays represented in the data set appear promising for building a defined approach for eye irritation testing. However, prospective *in vitro* testing would be needed to fill data gaps before a definitive approach could be identified. This testing will begin in early 2018 and will be coordinated by a validation management team comprised of ICCVAM Ocular and Dermal Irritation Workgroup members, NICEATM staff, and representatives from industry and animal welfare organizations.

Skin Sensitizer Testing

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

Widely used test methods for detecting ACD hazard potential of chemicals use guinea pigs or mice. However, international restrictions on animal testing for cosmetics and other products and an advanced mechanistic understanding of the adverse outcome pathway for skin sensitization are driving interest in non-animal test methods.

ICCVAM/NIEHS: Defined Approaches for Identifying Skin Sensitizers

NICEATM and ICCVAM scientists developed a defined approach that uses data from three *in vitro* tests -- the direct peptide reactivity assay (DPRA), human cell line activation test (h-CLAT), and KeratinoSens 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 particular combinations of inputs and machine learning approaches yielded more accurate predictions of LLNA or human skin sensitization hazard than any of the *in chemico*, *in vitro*, or *in silico* methods alone. This effort was described in three journal articles that each focused on different strategies and targets:

- The first article described how the defined approach used computer algorithms to integrate data to predict LLNA outcomes.
- The second article described the use of data from human exposures to predict human skin sensitization hazard.
- Further development of this approach predicted human or animal skin sensitization potency, enabling the classification of skin sensitizers as weak or strong without animal tests.

CPSC/NIEHS/NIOSH/NIST: Validation Study of the Electrophilic Allergen Screening Assay

The electrophilic allergen screening assay (EASA) is a chemical assay that measures light absorbance or a fluorescent signal in proportion to a chemical's tendency to bind to probe chemicals that mimic proteins. Binding of a chemical to skin proteins is the first step in the development of ACD. A validation study of the EASA began in 2017, with four ICCVAM agencies participating in the study. NICEATM is coordinating the study and members of the ICCVAM Skin Sensitization Workgroup are serving on the study management team. Efforts in 2017 focused on testing a small group of blinded chemicals for a preliminary assessment of accuracy and reliability; the study is expected to run through the end of 2018.

NIEHS: Assessment of Variability in Human Skin Sensitization Data

Ideally, alternative models developed to identify potential human skin sensitizers are evaluated using human skin sensitization data. However, human skin sensitization tests on the same chemical can produce variable results. This can make assessment of alternative models extremely challenging. NICEATM is using human skin sensitization data in the Integrated Chemical Environment and data obtained via industry consortia to compile a data set to better characterize the variability of human skin sensitization data.

NIEHS: Testing to Expand the Applicability Domain of a Defined Approach for Identifying Skin Sensitizers

NTP is coordinating testing of more than 200 chemicals nominated by ICCVAM agencies to expand the chemical space coverage for a defined approach for identifying skin sensitizers. The nominated chemicals all have existing LLNA data and include pesticides, formulations, industrial chemicals, and other chemicals of interest to ICCVAM agencies. Chemicals are being tested using three *in vitro* test methods that map to key events in the skin sensitization adverse outcome pathway. Testing began in 2016 and is scheduled to be completed in 2019. The data from this study will enable an evaluation of the appropriateness of a defined approach using these three *in vitro* methods for various regulatory applications.

NIEHS: Evaluation of Defined Approaches to Identify Skin Sensitizers

NICEATM collaborated with the Cosmetics Europe Skin Tolerance Task Force to evaluate defined approaches for prediction of skin sensitization hazard submitted to the Organisation for Economic Co-operation and Development (OECD). NICEATM has evaluated six defined approaches against a set of previously untested chemicals with *in vitro* and *in silico* data provided by Cosmetics Europe. Journal articles describing the data sets and the performance of the defined approaches will be published in 2018.

In a related effort, a joint proposal to develop a performance-based test guideline for defined approaches to skin sensitization testing and assessment, developed collaboratively by ICCVAM, NICEATM, and ICATM partners (Health Canada and EURL ECVAM), was submitted to the OECD in 2016 and included on the OECD workplan in 2017.

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.

EPA/FDA/NIEHS/NIH: Tox21 Activities

The interagency Tox21 research initiative uses *in vitro*, HTS assays to test a broad variety of substances and considers data from the screenings collectively to assess effects on biological pathways related to toxicity.

The tenth anniversary of Tox21 was observed in 2017. The program's accomplishments during that time included use of knowledge gained through Tox21 to inform policy and regulatory decisions about chemical safety; the publication of more than 200 peer-reviewed articles; and the public availability of millions of data points for research and analysis.

As Tox21 enters its second decade, its new strategic plan features five areas of focus:

- Develop and deploy alternative test systems to predict human toxicity and dose response
- Address technical limitations of current *in vitro* test systems
- Curate and characterize legacy *in vivo* toxicity data as a resource for interpreting Tox21 data
- Develop a framework for efficient validation of Tox21 approaches
- Refine and deploy *in vitro* methods for characterizing pharmacokinetics to increase predictivity and reduce uncertainty

Tox21 sponsored the Transform Tox Testing Challenge, which recruited innovative thinkers to find new ways to incorporate chemical metabolism into HTS assays. The goal was to help researchers more accurately assess effects of chemicals and better protect human health.

The first stage of the challenge, launched in January 2016, culminated in a July 2016 workshop, which brought together the 10 Stage 1 challenge winners and other experts to discuss the Tox21 and ToxCast programs, the Stage 1 proposals, and feasible expectations for the remainder of the challenge.

The goal of Stage 2 of the challenge was to encourage the Stage 1 winners to further develop their proposals into practical designs for new chemical screening technologies. Stage 2 winners were announced in November 2017. A third stage of the challenge, which would promote commercial development of the technologies, is currently under consideration.

DOD: ADMET Center of Excellence

The U.S. Army continues to explore approaches to reducing animal use in development of medical countermeasures to chemical and biological threats. The Absorption, Distribution, Metabolism, Elimination, and Toxicology Center of Excellence (ADMET CoE) has instituted best practices from the pharmaceutical industry to address this goal. Novel chemical compounds identified as potential therapeutics in target-specific high-throughput and virtual assays are characterized using validated *in silico* and *in vitro* assays to predict potential to become a FDA-approved drug. These cost-effective assays identify compounds with unfavorable properties, which are eliminated prior to animal testing. Assays to predict plasma stability, microsomal stability, cytochrome p450 inhibition (drug-drug interaction), intestinal and blood-brain barrier permeability, and liver toxicity have been validated, and data have been generated for more than 165 chemical compounds to date. Compounds with favorable ADMET profiles can then be transitioned to second tier *in vitro* testing for cardiotoxicity, advanced liver toxicity, metabolite identification, and protein binding.

DOD: Rapid Threat Assessment Program

Using current approaches, it can take months or years to understand the mechanism of action for new drugs or toxic agents, leaving personnel at risk of exposure to these agents unprotected in the meantime. To address this need, the Defense Advanced Research Projects Agency established the Rapid Threat Assessment program. The program's goal is to use new high-throughput analytics and mass spectrometry approaches to reduce the time needed to understand a new chemical's mechanism of action to 30 days. In addition to rapidly providing information on potential toxicity of new chemicals, the approach is expected to reduce the need for animal tests. A proof-of-concept study using this approach successfully identified the mechanism of action of the nitrogen mustard chemotherapeutic agent bendamustine. This five-year partnership with three academic laboratories is scheduled to conclude in late 2018 and will result in publications of methods and techniques.

DOD: Microphysiological Systems Program

The Defense Advanced Research Projects Agency's human-on-a-chip project is developing a microphysiological organ systems platform to evaluate the efficacy and safety of medical countermeasures to toxic agent exposures. This platform includes components representing

10 human physiological systems that interact with each other in a physiologically relevant manner, while maintaining tissue viability for at least four weeks. FDA has been involved in this program from the beginning to ensure that regulatory challenges of drug safety and efficacy review are considered during development. The program will conclude in 2018, and avenues for commercializing the platform are anticipated via Emulate, Inc., and CN Bio Innovations.

DOD: Ex Vivo Countermeasure Evaluation and Licensure Program

The Defense Threat Reduction Agency's *Ex Vivo* Countermeasure Evolution and Licensure (XCEL) program develops microphysiological systems to evaluate chemical and biological threat agent assessment and medical countermeasure research and development. XCEL is developing four human primary cell-based organ systems (liver, heart, lung, and kidney/blood vessel) that will be integrated into a platform that includes a blood surrogate, interlinked microfluidics (channels, pumps, and valves), in-line sensors, and off-line analytics with on-board data integration. The lung component of the system, known as the Pulmonary Lung Model, or PuLMo, was recognized by R&D 100 Magazine as a Top 100 Technology Development for 2016. Current efforts are focusing on partial validation of the platform by live testing with known threat agents and toxic drugs.

DOD: Cellular Sentinels of Toxicity Platform

Occupational and environmental chemical exposures in deployment and training are the most challenging aspects of DOD risk management. Toxicology studies depending on animals are ill-equipped to meet the critical and growing need for data to inform risk management. To address this need, USAF research scientists collaborated with Sanford Burnham Prebys to develop the Cellular Sentinels of Toxicity Platform (CSTP), a suite of HTS assays for cellular phenotype and physiology. CSTP builds upon other high-throughput toxicity screening efforts like ToxCast and Tox21 in two ways. First, CSTP assays utilize human-induced pluripotent stem cells, which more accurately reflect the physiology of mature cells than traditional immortalized cell lines, and thus provide more relevant models for interrogating the effects of potentially toxic agents on the human nervous system, heart, and liver tissue. Second, CSTP combines functional analyses such as cellular impedance and phenotypic readouts that do not require the engineering of genetic constructs to report on

cellular function. These assays allow for the early assessment of potential toxicities in a rapid, cost-effective manner that will simultaneously improve the relevance of the data produced while reducing the downstream use of animal studies.

DOD: Identification of Genetic Elements Underlying Toxic Responses

With the goal of unbiased characterization of genetic influence in toxicological exposure risk, USAF scientists developed a high-content assay in which genetically characterized cell lines were treated with a test panel of toxicants. This project, initiated in 2016, is aimed at developing personalized prediction and response of toxicological field exposures, a critical DOD focus area. More than 11,000 morphological features on every cell in the assay were measured, and novel software was developed to identify subsets of these features that can identify exposure to different compounds. During 2016 and 2017, nearly 300 cell lines were screened using high-throughput microscopy, and software was developed to analyze the images, measure and optimize phenotypic features, and identify genetic elements underscoring different toxicological responses. The completion and validation of this assay will enable targeted and sophisticated characterization of toxicant exposure in model cell lines representing any tissue in the human body, thus reducing or eliminating the need for animal studies.

DOD: High-content In Vitro Assays and Computational Models to Inform Human Health Risk Assessment

The USAF used high-content *in vitro* models to obtain data on a large number of chemicals that are relevant to the USAF occupational exposure, either for ground crews maintaining or repairing aircraft or aircrew members during flight. These *in vitro* cellular systems may inform potential toxicity hazards of hundreds to thousands of chemicals for which there is limited, or no, specific endpoint. Assays using immortal and human stem cells have been used to test thousands of chemicals at many different doses, supporting a mechanistic understanding of toxicity and providing input to quantitative structure-activity relationship (QSAR) and pharmacokinetic models. Recently, advanced algorithms utilizing QSAR and read-across techniques have been applied to Tox21/ToxCast data sets and data from USAF studies using human nervous system stem cells. The goal of these studies is to derive a rapid assessment tool to determine if chemicals measured in the USAF airman breathing space could result in neurological or cognitive effects. Similar approaches have been applied to

data sets from a number of chemical toxicological databases to target follow-up studies on only those chemicals having highest toxicity potential.

FDA: Collaboration with Emulate, Inc., to Develop Organ Chips for Toxicity Testing

In April 2017, FDA announced a multiyear research and development agreement with Emulate, Inc., to evaluate the company's organs-on-chips technology in laboratories at the FDA Center for Food Safety and Applied Nutrition. The project will focus first on developing a liver chip, but the agreement may expand in the future to develop kidney, lung, and intestine models. The ultimate goal is to more precisely predict how specific organs will respond to potential chemical hazards found in foods, cosmetics, or dietary supplements than with current methods. More details about the agreement are available in an FDA blog article by FDA ICCVAM representative Suzanne Fitzpatrick, Ph.D.

FDA: Rapid Risk Assessment of Medical Device Leachables

Medical device materials contain substances that can produce adverse health effects in patients if released from the device in sufficient quantities. Historically, the potential for health hazards to occur due to the release, or leaching, of these substances from the device was evaluated primarily through animal testing. However, a chemical characterization/risk assessment approach is being increasingly used to assess the potential for adverse systemic effects to occur in patients due to leaching from medical devices. A key component of this approach is exposure assessment; however, data are often unavailable on the amount of the leachables released from medical devices and taken up by the patient. To address this data need, the FDA Center for Devices and Radiological Health (CDRH) is developing computational models to predict patient exposure to compounds released from polymeric materials and have developed a software tool to automatically compare the computer-derived exposure estimate to acceptable exposure limits for the compounds. Based on this comparison, the toxicological risk posed to a patient by any leachable substance can be rapidly assessed, obviating the need for animal testing to assess these biocompatibility endpoints. In 2016, this project focused on developing a computational model to predict the release of color additives from various polymers and to compare the predicted patient exposure to tolerable intake values for the color additives. A beta version of the computational tool was piloted by industry stakeholders in 2017, and the computational

model was described in three peer-reviewed journal articles published in 2017 (Chandrasekar et al., 2017a; Chandrasekar et al., 2017b; Janes et al. 2017). Future work will expand the exposure model to include other types of device leachables.

FDA: Best Practices for Characterizing Medical Device Extractables for Biocompatibility Risk Assessments

Extractables are substances that can be released from a medical device or material using solvents or conditions that are expected to be at least as aggressive as the conditions of clinical use. These substances can produce adverse health effects in patients if released from the device in sufficient quantities as leachables. A chemical characterization/risk assessment approach is being increasingly used for the biological safety assessment of medical devices, which is expected to reduce use of animals for toxicity and biocompatibility testing. A key component of this approach is the extraction of the device in various solvents, followed by identification and quantification of the extracted compounds. The toxicological safety of the device is then determined by comparing the amount of each compound extracted to an acceptable level of exposure. One limitation of this approach is the lack of clear guidance for conducting the extraction of the device and chemical analysis of the extracts. To address this limitation, in 2017, CDRH began conducting strategic scientific studies that will enable FDA to recommend optimal analytical methods to conduct these chemical analyses. Analytical conditions are being optimized for chemical characterization of a group of six device materials. Optimization includes, but is not limited to, extraction conditions and utilization of up-to-date reference data for identification of extractables and quantification using internal surrogate standards. CDRH organized three seminars within FDA to share initial findings, which will also be presented at the Society of Toxicology meeting in March 2018 (Sussman et al.). This work will improve public health outcomes while reducing the costs for industry in delivering safe and effective medical devices/technologies to market.

NIEHS/NIH: Evaluation of FXR active Chemicals Identified from Tox21 Screening

Scientists at NICEATM and the NIH National Center for Advancing Translational Sciences (NCATS) and academic and commercial collaborators used four experimental approaches to better characterize compounds identified in Tox21 quantitative HTS assays as having farnesoid X receptor alpha agonist or antagonist activity. The study generally confirmed the Tox21 results, provided orthogonal data on protein-to-protein interactions and receptor

docking, and translated those results to an *in vivo* system (larval medaka assay). The study, which will be presented at the 2018 Society of Toxicology meeting (Hamm et al.), demonstrates an approach to evaluate compounds that show activity in HTS.

NIH: Tissue Chip Initiatives and Projects

NCATS is leading the Tissue Chip for Drug Screening program in collaboration with other federal government offices to develop human tissue chips. Tissue chips that accurately model the structure and function of human organs will help predict drug safety in humans more rapidly and effectively. The current focus of the program is toxicity testing.

In 2014, NIH and the Defense Advanced Research Projects Agency funded 11 academic laboratories for the second phase of the Tissue Chip for Drug Screening program. The goal of this phase, which concluded in 2017, was to integrate chip devices into a full body system to evaluate drugs and diseases. As part of this program, NCATS established three Tissue Chip Testing Centers in October 2016. The goals for the Tissue Chip Testing Centers include providing the means for scientists participating in the Tissue Chip for Drug Screening program to test and validate tissue chip platforms independently; ensuring wide-ranging availability of tissue chip technology, particularly for regulatory agencies and pharmaceutical companies; and promoting adoption of this technology by the broad research community.

In October 2016, NCATS and the Center for the Advancement of Science in Space announced a funding opportunity to create tissue-on-chip and organ-on-chip platforms that mimic human physiology under the extreme environment of space. Five initial two-year awards were issued in June 2017. The goal of the Tissue Chips in Space initiative is to create tissue-on-chip and organ-on-chip platforms that can be sent to the International Space Station United States National Laboratory (ISS-NL) so that scientists can better understand the role of microgravity on human health and diseases and translate those findings to improve human health on Earth. During the first phase of the initiative, researchers will develop and test tissue chips on the ISS-NL in a microgravity environment. In the second phase, they will further demonstrate the functional use of the tissue chip models for more defined experiments on the ISS-NL.

NIST: Standardization of Cell-based Toxicity Assays for Testing of Nanomaterials

Cytotoxicity assays are commonly employed as screening tools to identify potential hazards associated with new chemicals and materials. These assays can reduce the need for animal testing in industrial manufacturing. Although cytotoxicity assays are used to evaluate biological effects associated with engineered nanomaterials, several studies that suggest the unique properties of nanomaterials, such as their high surface-to-volume ratio and small size, contribute to significant variability in the assay results. Thus, the need to improve cell-based toxicity assays for nanomaterials is broadly recognized.

To address this problem, National Institute of Standards and Technology (NIST) scientists used the MTS cell viability assay as a model system. A standard operating procedure for a 96-well assay was developed that included cell line identification testing, dosing preparation, and prescribed pipetting procedures. The protocol incorporates a measurement system that included in-line process controls for reagent quality, cell seeding quality, cell function, and nanomaterial interference. Execution of the protocol produces a value characterizing test nanoparticle toxicity and six additional measurements that characterize the measurement system.

The measurement paradigm was tested in an international study including laboratories from Switzerland, Thailand, the European Union, and Korea. The results indicated several sources of variability in the assay protocol and suggested performance specifications. The study highlighted the critical importance of cell line identification, consistent protocols for rinsing attached cell layers, and detailed nanoparticle dispersion techniques to obtain consistent, reproducible results in these assays. These findings were reflected a final draft international standard, ISO/DIS 19007: Nanotechnologies – In vitro MTS assay for measuring the cytotoxic effect of nanoparticles, which will be published in 2018.

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.

EPA: Implementation of Alternatives Directives in Lautenberg Chemical Safety Act

In June 2016, the U.S. Congress passed the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which amended the Toxic Substances Control Act, the primary chemicals management law in the United States. A key provision of the Lautenberg Chemical Safety Act required the EPA to develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing. EPA collected public comment on draft goals and objectives for the strategic plan during the second half of 2017, an effort that included a public meeting convened in November 2017 at NIH. A first draft of the strategic plan will be completed by March 2018, with the final to be published by June 2018.

EPA: Granting of Waivers for Toxicity Studies

The EPA Hazard and Science Policy Committee supports implementation of the vision of the 2007 National Academy of Science report, Toxicity Testing in the 21st Century. One approach being taken is to waive toxicity studies that do not provide useful information. The committee reviews data waiver requests for a variety of toxicity studies, primarily immunotoxicity, acute and subchronic neurotoxicity, developmental, reproductive, and subchronic inhalation toxicity studies, and grants waivers where appropriate to avoid unnecessary testing.

- In Fiscal Year 2016 (October 2015-September 2016), waivers were granted for 153 of 180 requests resulting in savings of about 44,000 animals and over $16 million in the cost of conducting the studies.
- In Fiscal Year 2017 (October 2016-September 2017) waivers were granted for 70 of 78 requests resulting in savings of about 41,000 animals and approximately $10.4 million in the cost of conducting the studies.

EPA/FDA/NIH/NIEHS: National Academies Report on Using 21st Century Science to Improve Risk-related Evaluations

A report released in January 2017 by the National Academies of Sciences, Engineering, and Medicine makes recommendations on the best ways to incorporate emerging science into risk-based evaluations of chemical safety. The report, Using 21st Century Science to Improve Risk-related Evaluations, was prepared at the request of the four Tox21 partner

organizations: NTP at NIEHS, EPA, NCATS, and FDA. The new report discusses both the inherent opportunities and the challenges that will need to be met to achieve the vision described in two earlier National Research Council reports, Toxicity Testing in the 21st Century and Exposure Science in the 21st Century.

FDA: Predictive Toxicology Roadmap

In December 2017, FDA announced publication of FDA's Predictive Toxicology Roadmap for integrating predictive toxicology methods into safety and risk assessments.

The Predictive Toxicology Roadmap presents a framework for new or enhanced FDA engagement in the science of toxicology that includes six elements:

1. An organizing committee to help identify areas where research is needed and reduce duplication of efforts
2. Training in use of new test methods
3. Communication among the Agency, sponsors, and test method developers
4. Fostering collaborations across sectors and disciplines nationally and internationally
5. Research to identify data gaps and promote promising technologies
6. Oversight to track progress

FDA plans a workshop for 2018 to support efforts to foster opportunities for sharing ideas, discussing new technologies, and highlighting collaborations to develop and test new methods. A post on the FDA Voice blog provides links to the Predictive Toxicology Roadmap and related activities.

FDA: Updated ICH Guidances on Toxicokinetics and Reproductive Toxicity

The FDA participates on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH brings together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of drug registration. The organization plays an important role in ensuring that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.

During 2016 and 2017, FDA collaborated with ICH partners to develop and update two guidance documents for safety testing with 3Rs relevance.

- ICH S3A Guidance: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies—Questions and Answers facilitates interpretation of S3A Guidance: The Assessment of Systemic Exposure in Toxicity Studies, especially to address the benefit and use of microsampling techniques to reduce and refine animal use in these studies. The Q&A guidance is intended to provide points to consider before incorporating microsampling techniques into toxicokinetic studies, and acknowledges the benefits (and some limitations) of their use. FDA requested public comment on the draft Q&A guidance in September 2016. A final version of the document is expected to be issued in 2018.
- ICH S5(R3), Detection of Toxicity to Reproduction for Human Pharmaceuticals, clarifies the qualification and potential use of alternative assays to assess reproductive risk and includes a list of compounds suggested for qualification of assays. In November 2017, FDA requested data on potential additional compounds to be added to the list. FDA will be accepting comments on the draft guidance through February 2018.

FDA: Updated Guidance on Biocompatibility of Medical Devices

The FDA Center for Devices and Radiological Health (CDRH) is continuing to expand acceptance of alternative information and non-animal testing to support biocompatibility evaluations of medical devices.

- In June 2016, CDRH published a Final Guidance on Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. This guidance highlights the concept that a biocompatibility assessment should begin with a risk-based approach instead of immediately considering new testing. If testing is needed, the guidance explains when *in vitro* tests can be substituted for *in vivo* thrombogenicity evaluations, and when chemical characterization and toxicological risk assessment can be substituted for *in vivo* systemic toxicity assessments. A webinar was held on July 21, 2016, to answer questions on this guidance, and the slides, audio presentation, and transcript can be found on the FDA website.

- In August 2017, CDRH published a Final Guidance on Qualification of Medical Device Development Tools. This guidance explains how new tools can be developed and qualified for a specific context of use, so that qualified tools can be used to support regulatory submissions to CDRH. The policy outlined in the guidance is applicable to *in vitro* models to replace animal testing where appropriate. A webinar was held on August 24, 2017, to answer questions on the guidance, and the slides, audio presentation, and transcript can be found on the FDA website. As tools become qualified under CDRH's Medical Device Development Tool program, they will be published in the Medical Devices section of the FDA website.

NIEHS: Grants Supporting Alternative Methods Development

NIEHS offers grants to U.S. small businesses to support development of novel testing approaches using state-of-the-art technologies. Some of this funding is provided through an omnibus solicitation of grant applications offered by the U.S. Department of Health and Human Services. Grants awarded under this program support development of cell-based assays to assess eye irritation, neurotoxicity, cardiotoxicity, skin and eye corrosivity, and DNA damage, as well as organotypic assays to assess cardiotoxicity, hepatotoxicity, and male reproductive toxicity.

During 2016 and 2017, NIEHS also issued the following Requests for Application for grants targeted towards specific testing applications:

- Validation and Commercialization of Approaches to Reduce Animal Use in Toxicology Testing: this opportunity supports development of *in vitro* assays, quantitative structure-activity relationship models, and computational methods to predict toxicity. Priority areas include ocular toxicity, developmental toxicity, carcinogenicity, and acute toxicity testing. A grant awarded through this program is currently supporting development of an *in vitro* human airway model for regulatory toxicity testing.
- Novel Assays for Screening the Effects of Chemical Toxicants on Cell Differentiation: this opportunity supports development of assays to provide

information on mechanisms of chemically induced biological activity and potentially inform the role of genetic diversity in toxicological effects.

- Organotypic Culture Models Developed from Experimental Animals for Chemical Toxicity Screening: this opportunity supports development of systems that will facilitate comparisons between *in vivo* and *in vitro* test results.

More information about NIEHS small business grants is available on the NIEHS website. Current funding opportunities are listed on the NTP website.

NLM: Update of ToxTutor

In October 2016, the National Library of Medicine (NLM) released an extensive update of its 20-year-old online ToxTutor course. ToxTutor is a self-paced tutorial for users of toxicology resources, including NLM chemical and toxicological databases. The 2016 update incorporated advances in the science of toxicology, provided more information on alternatives to animal testing, and featured responsive design to support use on mobile devices. Additional content was added in September 2017 and included sections covering basic physiology, toxicokinetics, absorption, distribution, biotransformation, excretion, and cellular toxicology. If a certificate of completion is needed, the tutorial can be completed through a free learning management system. ToxTutor is being used in academic courses, for training in companies and elsewhere, and is approved for some continuing education contact hours. Additional topics will be included in future updates.

Outreach and Collaborative Activities

ICCVAM strengthened ties with U.S. and international collaborators in 2016 and 2017 by sponsoring meetings and webinars and collaborating with other national validation organizations. ICCVAM also actively engaged stakeholders during development of the U.S. strategic roadmap.

Development of the U.S. Strategic Roadmap

During 2017, ICCVAM coordinated the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. The U.S. Strategic Roadmap was developed with participation from all ICCVAM member agencies and multiple interagency workgroups, and with input from a broad range of stakeholder groups.

The roadmap describes a new framework for the safety testing of drugs and chemicals, which aims to provide more human relevant toxicology data while reducing the use of animals. The successful development and implementation of these new approaches will require coordinated efforts that address three strategic goals:

- Connecting end-users with developers of new approach methodologies
- Fostering the use of efficient, flexible, and robust practices to establish confidence in new methods
- Encouraging the adoption and use of new methods and approaches by federal agencies and regulated industries

The roadmap was first proposed to the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) in 2015. SACATM expressed support for the development of the roadmap as an ICCVAM activity at its 2016 meeting. A meeting of ICCVAM members and other federal employees in February 2017 established an outline for the roadmap. Opportunities for public comment during development of the roadmap occurred during the annual meeting of the Society of Toxicology in March; the ICCVAM Public Forum in May; the NTP Board of Scientific Counselors meeting in June; and the SACATM meeting in September.

The final roadmap document was published in January 2018 and is available on the NTP website.

Activities are already underway to address the roadmap goals, some of which are described elsewhere in this document. Presentations at the September 2017 SACATM meeting described implementation of the roadmap for acute systemic toxicity, eye and skin irritation, and skin sensitization testing. Reviews of U.S. agency information requirements for all of these areas are being prepared and are planned for publication in 2018.

Public Forums

ICCVAM held two public forum meetings in 2016 and 2017. These meetings provided an opportunity for public interaction with representatives from ICCVAM member agencies.

- View materials from the 2016 Public Forum
- View materials from the 2017 Public Forum

ICCVAM held its third public forum on May 25, 2016, at NIH in Bethesda, Maryland. This meeting was attended by more than 150 individuals in person and remotely, and provided an opportunity for public interaction with representatives from ICCVAM member agencies. ICCVAM representatives provided information about their agencies' activities relevant to the development and use of alternative test methods. Comments from stakeholder groups praised recent progress by ICCVAM and member agencies toward replacing required animal tests with alternatives. Several commenters suggested future activities and areas for increased focus.

The 2017 public forum was held on May 23 at NIH in Bethesda. Twelve public participants and about 50 webcast viewers joined more than 30 government employees representing 10 ICCVAM member agencies. Representatives of the attending ICCVAM member agencies described internal and collaborative activities to advance development and acceptance of alternative methods. Presentations at the meeting also discussed ongoing development of the U.S. strategic roadmap, which was also the focus of most of the public comments submitted for the meeting.

ICCVAM Communities of Practice Webinars

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 second of these webinars, presented on Jan. 26, 2016, was titled Fundamentals of Using Quantitative Structure-Activity Relationship Models and Read-across Techniques in Predictive Toxicology. The webinar, which was viewed by over 250 people, focused on applications of methods that use chemical structure, properties, and toxicity data to predict characteristics of untested chemicals. Alex Tropsha, Ph.D., University of North Carolina at Chapel Hill, provided an overview of how quantitative structure-activity relationship models are used in this context. Louis (Gino) Scarano, Ph.D., of the EPA Office of Pollution Prevention and Toxics, reviewed how the EPA uses quantitative tools and models to generate predictions of toxic effects of new chemicals, which can then be used to make occupational risk assessments and identify where further testing might be needed.
- Nearly 200 viewers attended the Jan. 24, 2017, Communities of Practice webinar, Incorporating Chemical Information: Resources, Limitations, and Characterizing the Domain of Applicability for 21st Century Toxicity Testing. This webinar emphasized the importance of understanding the structural and functional diversity of chemical sets used in developing and validating alternative approaches to traditional *in vivo* toxicology test methods. Presentations by Denis Fourches, Ph.D., of North Carolina State University, and Kamel Mansouri, Ph.D., of the EPA National Center for Computational Toxicology, featured next-generation chemoinformatics techniques that are being used to fully characterize chemical lists, as well as case studies where such techniques have been successfully applied.

Agency-Sponsored Workshops and Webinars

ICCVAM agencies presented a number of workshops and webinars during 2016 and 2017 to foster collaboration and provide information about alternative testing methods, summarized in the table below.

Meeting Date and Location	**Sponsoring Agency (and partner organization)**	**Meeting Title (with link to page if available)**	**Meeting Summary**
Feb. 17-18, 2016 RTP, North Carolina	NIEHS, EPA	*In Vitro* to *In Vivo* Extrapolation for High Throughput Prioritization and Decision Making	Participants in the workshop (1) reviewed the state of the science to form recommendations on the best practices for using IVIVE in chemical screening and risk decision making, (2) identified areas that require additional data and/or research, and (3) highlighted examples of how best to apply IVIVE in a tiered risk decision-making strategy.
March-Sept. 2016 Online/Bethesda, Maryland	NIEHS (PETA International Science Consortium)	Alternative Approaches for Acute Inhalation Toxicity Testing	The webinar series explored and discussed alternative approaches that could replace, reduce, or refine the use of animals for identifying chemicals that may cause acute systemic toxicity when inhaled. The subsequent workshop developed recommendations for advancing new approaches for acute inhalation toxicity testing.
April 5-6, 2016 College Park, Maryland	FDA, NIH/NCATS	Assay Development for High Throughput Screening	This workshop for scientists involved in assay development for HTS and lead optimization shared best practices and provided advice on robust assay design.
June 20, 2016 Bethesda, Maryland	NIH	Bioinformatics Symposium	Attendees at this symposium learned how scientists are using software licensed by the NIH Library Bioinformatics Support Program to analyze, integrate, and annotate data from multiple genomics technologies.
July 8, 2016 RTP, North Carolina	EPA, NIEHS, NIH/NCATS	Transform Tox Testing Challenge Workshop	This workshop featured presentations by Stage 1

Meeting Date and Location	Sponsoring Agency (and partner organization)	Meeting Title (with link to page if available)	Meeting Summary
			winners of the Transform Tox Testing Challenge and provided opportunities to discuss the remainder of the challenge.
July 21, 2016 Online	FDA/CDRH	Final Guidance on "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	The FDA held this webinar for industry to review the recommendations in this final guidance and to clarify and update how medical device developers may use ISO 10993-1 standard in their premarket submission to determine the potential for an unacceptable adverse biological response resulting from contact of a medical device with the body.
Sept. 6, 2016 Online	NIH/NCATS	Tissue Chips in Space Initiative	This webinar, intended for interested investigators, provided an overview of a program to use organ-on-chip platforms to better understand the molecular and cellular basis of human disease in microgravity.
Sept. 16, 2016 Bethesda, Maryland	NIH (PLoS Computational Biology)	Computational Biology: Past, Present, and Future	This overview of current topics in computational biology featured two discussion panels on near-term challenges and opportunities in the field and how computational biology and computing in general will affect human health.
Dec. 8, 2016 Online	NLM	Introduction to ALTBIB	This webinar described and demonstrated the use of ALTBIB, NLM's online resource for alternatives to vertebrate animal use in research and testing.
February-March 2017 Online	NIEHS	Using Informatics to Improve Data Analysis of Chemical Screening Assays Conducted in Zebrafish	This webinar series considered how issues of variability in zebrafish toxicological screening studies might be addressed by use of standardized

Meeting Date and Location	**Sponsoring Agency (and partner organization)**	**Meeting Title (with link to page if available)**	**Meeting Summary**
			nomenclature systems, also known as ontologies.
June 26-27, 2017 Bethesda, Maryland	NIEHS (Human Toxicology Project Consortium)	BioMed21: A Human Pathways Approach to Disease Research	This workshop brought representatives from international projects investigating adverse outcome pathways, with the goal of developing recommendations toward fully implementing a human systems-biology platform for understanding disease and improving interventions.
August 24, 2017 Online	FDA/CDRH	CDRH Final Guidance: Qualification of Medical Device Development Tools	The FDA hosted this webinar for tool developers and stakeholders interested in learning more about the guidance document and the Medical Device Development Tools program.
August-September, 2017 Online	NIEHS	Approaches to Genomic Dose-Response Modeling	This webinar series featured four government and academic research groups describing their approaches to genomic dose-response modeling, which uses toxicogenomics data for risk assessment applications.
Oct. 24, 2017 College Park, Maryland	FDA (Society of Toxicology)	*In Vitro* to *In Vivo* Concordance for Toxicity Prediction and Use in Safety Assessments	The latest in the series Colloquia on Emerging Toxicological Science: Challenges in Food and Ingredient Safety featured expert reviews on state-of-the-art *in vitro* technologies for safety assessment and how they are being utilized.
October-November 2017 Online	NIEHS and EPA	Superfund Research Program Risk e-Learning Seminars on Adverse Outcome Pathways	The webinar series examined how the adverse outcome pathway framework can help support greater use of mechanistic or pathway-based data in risk assessment and regulatory decision making.

Meeting Date and Location	Sponsoring Agency (and partner organization)	Meeting Title (with link to page if available)	Meeting Summary
Nov. 2, 2017 Bethesda, Maryland	NIEHS and EPA	Alternative Test Methods to Reduce Vertebrate Animal Testing under the Toxic Substances Control Act	EPA is developing a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing. This meeting provided an opportunity for public comment on the plan.
Nov. 14, 2017 Online	NIH/National Center for Advancing Translational Sciences	Securing SBIR & STTR Funding: Support for Entrepreneurs and Researchers in Biotech	This webinar provided an overview of programs and funding that support small businesses and technology transfer organizations, including those involved in the development of alternative testing approaches.
Nov. 28-30, 2017 Arlington, Virginia	EPA	Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways	This meeting of the Federal Insecticide, Fungicide, and Rodenticide Scientific Advisory Panel considered the use of high-throughput assays and computational models in the EPA Endocrine Disruptor Screening Program.

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 from the European Union, United States, Japan, Canada, and South Korea (see below). Brazil and China have been participating in ICATM since 2015 as observers.

ICATM meetings provide an opportunity for participant organizations to discuss activities in identified areas of cooperation. These interactions allow ICATM partners to develop good communications and working relationships in support of collaborative test method development. ICCVAM representatives participated in an ICATM coordination meeting in 2016.

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 related 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 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. Responsibility for Canada's participation in ICATM is transitioning to the Canadian Centre for the Validation of Alternative Methods (CaCVAM), which was established in 2017.
- **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.

ICATM Skin Sensitization Workshop

In October 2016, ICATM convened a workshop on International Regulatory Applicability and Acceptance of Alternative Approaches to Skin Sensitization Assessment of Chemicals. Workshop participants reviewed current international regulatory requirements for skin sensitization testing, including currently available non-animal approaches for this testing, and considered what steps should be taken to support regulatory acceptance of these approaches. A poster presented at the 2017 Society of Toxicology Meeting (Kleinstreuer et al.) summarized the workshop and its outcomes. A position paper developed from the workshop proposed practical ways to further promote the regulatory use and facilitate adoption of non-animal defined approaches for skin sensitization assessments. Another product of the workshop was a paper summarizing international regulatory requirements for skin sensitization testing, which will be published in 2018. Discussions at the workshop also formed the basis for a proposal to develop a performance-based test guideline for defined approaches for skin sensitization. The proposal was approved at the April 2017 meeting of the Working Group of National Coordinators of the Test Guidelines Programme of the Organisation for Economic Co-operation and Development (OECD) for inclusion in the OECD workplan.

Collaborations with International Validation Organizations

Representatives from JaCVAM, KoCVAM, and Health Canada attended the 2016 meeting of SACATM as nonvoting liaisons; representatives from KoCVAM and CaCVAM attended the 2017 SACATM meeting.

A NICEATM scientist participated on a EURL ECVAM Scientific Advisory Committee working group on eye irritation methods in May 2016.

The following ICCVAM workgroups had ICATM member liaison representatives during 2016 and 2017.

ICCVAM Workgroup	ICATM Organizations with Liaison Members
Acute Toxicity	EURL ECVAM, KoCVAM

ICCVAM Workgroup	ICATM Organizations with Liaison Members
Developmental and Reproductive Toxicity	EURL ECVAM, JaCVAM, KoCVAM
IVIVE	EURL ECVAM, JaCVAM
Ocular and Dermal Irritation	EURL ECVAM, Health Canada
Read-across	EURL ECVAM, JaCVAM
Reference Chemical	EURL ECVAM, Health Canada, JaCVAM, KoCVAM
Skin Sensitization	EURL ECVAM

NICEATM or ICCVAM scientists served on the management teams or peer review panels for the following JaCVAM-coordinated validation studies during 2016 and 2017.

- IL-8 *in vitro* test for assessing skin sensitization potential: study is complete; NICEATM staff served on the validation management team and an ICCVAM member served on the peer review panel.
- Vitrigel-EIT assay for eye irritation testing: study is complete; NICEATM staff served on the validation management team and an ICCVAM member served on the peer review panel.
- Hand1-luc *in vitro* test for assessing reproductive toxicity potential: study is complete; NICEATM staff served on the validation management team and an ICCVAM member served on the peer review panel.
- SIRC-CVS assay for eye irritation testing: study is complete; an ICCVAM member served on the peer review panel.
- Amino acid derivation reactivity assay for assessing skin sensitization potential: study is complete; a peer review is scheduled for spring 2018; NICEATM staff served on the validation management team and an ICCVAM member will serve on the peer review panel.
- Vitrigel-SST assay for assessing skin sensitization potential: study is on hold; NICEATM staff are serving on the validation management team.

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 Test Guidelines Programme of 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 35 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 Working Group of National Coordinators and in other test guideline development activities. Wanda Hall, EPA, has served as U.S. National Coordinator since 2015.

In addition to reviewing a number of test guidelines under revision during 2016 and 2017, NICEATM and ICCVAM collaborated with international colleagues on a revision of the acute dermal toxicity test guideline (Test Guideline 402) adopted by OECD in 2017. NICEATM and ICCVAM also collaborated with international colleagues on the following OECD activities:

- Drafting of a new proposal for a performance-based test guideline regarding defined approaches and test methods for skin sensitization submitted to OECD in fiscal year 2017 (work product of the 2016 ICATM Skin Sensitization Workshop)
- Drafting of a guidance document on integrated approaches to testing and assessment (IATAs) for eye irritation hazard potential
- Drafting of a guidance document on the reporting of defined approaches to be used within IATAs
- Contributing a case study to a guidance document on reporting defined approaches and individual information sources for skin sensitization

NICEATM staff members participated in the following OECD activities during 2016 and 2017:

- A peer review panel updating Test Guideline 442B for non-radiolabeled murine local lymph node assay methods.

- Expert meetings on skin sensitization and skin and eye irritation in November 2016 and November 2017. Participants at these meetings review and comment on draft test guidelines. Revisions based on the expert groups' recommendations are circulated to the OECD member countries and are ultimately considered for approval and formal adoption by the OECD Working Group of National Coordinators.
- Meetings in November 2016 and October 2017 of the OECD Validation Management Group-Non-animal. This international group focuses on evaluation of new methods for identifying endocrine disruptors.
- A special session of the OECD Working Group of National Coordinators in December 2017 to discuss the proposal for a new performance-based test guideline for defined approaches to skin sensitization testing and assessment.

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 NIEHS about ICCVAM activities. SACATM held public meetings on September 27, 2016, at NIEHS in Research Triangle Park, North Carolina, and September 18-19, 2017, at NIH in Bethesda, Maryland.

- Materials from past SACATM meetings
- Roster of SACATM members during 2016 and 2017

The 2016 SACATM meeting focused on broad questions relevant to development of a U.S. strategic roadmap for implementing new approaches to toxicity testing. Former NTP Associate Director John Bucher, Ph.D., provided an overview of traditional approaches to toxicity testing and issues that will need to be addressed to replace them with alternative approaches. Tim Malloy, J.D., University of California, Los Angeles, expanded on this latter point in a presentation summarizing results of a survey assessing drivers and barriers to implementation of alternative methods. NICEATM Deputy Director Nicole Kleinstreuer, Ph.D., presented a summary of NICEATM and ICCVAM activities. ICCVAM co-chair Anna Lowit, Ph.D., EPA, gave an update on activities relevant to the 2013 ICCVAM Vision and

Strategy, and Joanna Matheson, Ph.D., U.S. Consumer Product Safety Commission, provided a more detailed summary of ICCVAM activities in the area of skin sensitization.

The 2017 SACATM meeting was structured to obtain input on and stimulate discussion about the draft Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. Presentations and discussions during the majority of the two-day meeting focused on how to address the three strategic goals of the roadmap. Matheson and Kleinstreuer described initial activities to implement the roadmap goals in the areas of skin sensitization and acute toxicity, respectively. Updates on activities relevant to ICCVAM were provided by Mark Johnson, Ph.D. (U.S. Department of Defense); Russell Thomas, Ph.D. (EPA, focusing on Tox21 activities), and Louis Scarano, Ph.D. (EPA, focusing on implementation of the 2016 Lautenberg Chemical Safety Act).

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), which is supported by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

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. More recently, the term new approach methodologies has been adopted as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination of these that can be used to provide information on chemical hazard and risk assessment.

The ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-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."

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

- Increase the efficiency and effectiveness of federal agency test 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 NIEHS under the NTP Interagency Center for the Evaluation of Alternative Methods (NICEATM).

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 Institute of Standards and Technology (NIST)
- 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)
- 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)

New Agency Joins ICCVAM

In 2016, the National Institute of Standards and Technology (NIST) joined ICCVAM. This was the first time ICCVAM expanded its membership to include a new member agency since

its inception in 2000. NIST, which is part of the U.S. Department of Commerce, had been interacting with ICCVAM since 2015. The agency submitted an official request to join ICCVAM in January 2016, which was approved in February by NIEHS Director Linda Birnbaum, Ph.D.

NIST participation provides ICCVAM with interest and experience in the study of process controls, measurement artifacts, and interlaboratory testing. This will particularly benefit ICCVAM in the development of validation studies to assess the appropriateness of new test methods for specific purposes. Specifically, NIST has experience with cell-based and small model organism assays, which are becoming increasingly important as alternatives for traditional animal tests. NIST also brings to ICCVAM additional expertise in experimental design and statistical analysis.

ICCVAM Advisory Committee

The ICCVAM Authorization Act established the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). SACATM advises the Director of NIEHS, NICEATM, and ICCVAM about NICEATM and ICCVAM activities.

SACATM, which is directed by its charter to meet at least once each fiscal year, met in September 2016 and September 2017

- Summaries of 2016 and 2017 SACATM meetings
- Roster of SACATM members during 2016 and 2017

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

The Role of ICCVAM Workgroups

ICCVAM establishes temporary ad hoc workgroups to perform specific tasks identified by the committee as being important for the development or validation of new, revised, and alternative methods. The workgroups are chaired by representatives from agencies that use or require data from the topic of interest. The chairs are responsible for developing the group's scope and charge, which is then reviewed and approved by ICCVAM. ICCVAM member agencies and partners in the International Cooperation on Alternative Test Methods are then invited to participate in the workgroup.

ICCVAM workgroups provide a forum for agencies to share knowledge and ensure that agency priorities are considered in the course of addressing the duties listed above. It is envisioned that the workgroups will play a key role in implementing the goals of the Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States.

Alignment of ICCVAM Activities with ICCVAM Authorization Act

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. The table below notes how selected 2016-2017 ICCVAM and ICCVAM agency activities align with the ICCVAM duties as outlined in the ICCVAM Authorization Act

ICCVAM Duty	**Activity**
Review and evaluate new, revised, or alternative test methods	Management teams composed of NICEATM and ICCVAM agency scientists provided oversight and direction for three validation studies:

ICCVAM Duty	**Activity**
	the OptiSafe test method for eye irritation, the CertiChem *in vitro* test method to measure androgen receptor agonist and antagonist activity, and the EASA skin sensitization test method.
Facilitate appropriate interagency and international harmonization of test protocols that encourage reducing, refining, and replacing animal test methods	NICEATM scientists advised on validation studies conducted by Japan and the European Union. NIEHS held an expert discussion to support broader adoption of zebrafish for toxicological screening through increased standardization of protocols and nomenclature. NICEATM collaborated with the Cosmetics Europe Skin Tolerance Task Force to evaluate the defined approaches for assessment of skin sensitization hazard that have been submitted to the Organization for Economic Co-operation and Development (OECD). NICEATM and ICCVAM scientists participated in an ICATM-sponsored workshop, International Regulatory Applicability and Acceptance of Alternative Approaches to Skin Sensitization Assessment of Chemicals. The U.S. National Coordinator for the OECD Test Guidelines Programme is an *ex officio* member of ICCVAM and provides monthly updates on OECD activities.
Facilitate and provide guidance on validation criteria and processes	EPA and NIEHS conducted an evaluation of variability in LD50 data used as reference data for alternative methods. EPA and NIEHS compiled reference data from rodent studies for use in validating alternative methods for identifying endocrine disruptors.
Promote the acceptance of scientifically valid test methods	EPA published Process for Establishing and Implementing Alternative Approaches to Traditional *In Vivo* Acute Toxicity Studies for FIFRA Regulatory Use. EPA is developing a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing. FDA published a Predictive Toxicology Roadmap for integrating predictive toxicology methods into safety and risk assessments.
Promote awareness of accepted test methods	USDA published a notice of an available exemption to reduce hamster use for leptospirosis vaccine testing. FDA published guidance and presented a webinar on pretesting evaluation and use of *in vitro* tests for biological evaluation of medical devices. NLM updated its online ToxTutor course to provide more information on alternatives to animal testing. Various ICCVAM agencies held workshops and webinars to share information and promote awareness of alternative methods. NICEATM and ICCVAM presented on 3Rs topics and activities at scientific meetings and other venues.
Prepare reports on ICCVAM progress and accomplishments under the Act and make them available to the public	ICCVAM published ICCVAM Biennial Progress Report 2014-2015. ICCVAM agencies provided updates at 2016 and 2017 ICCVAM public forum meetings.

How NICEATM Supports ICCVAM

NICEATM, an office within the NIEHS Division of NTP, 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 NTP 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

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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 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.

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 Center for Advancing Translational Sciences (of the National Institutes of Health)

Reference Pages

Agency Representatives in 2016 and 2017

Types of representatives:

- The **Principal Agency Representative** is the primary source of communication from his or her agency to the committee and NICEATM. He or she regularly attends all ICCVAM meetings and teleconferences, coordinates participation of other representatives from the agency, and casts the agency's vote on occasions when formal voting is required.
- **Alternate Agency Representatives** participate in ICCVAM committee activities in place of the Principal when necessary.
- An agency may designate one or more **Other Agency Representatives** to participate in ICCVAM to provide broader representation or expertise.

Agency (Office)	Representative	Representative Type (as of December 2017)	Service Continuing Into 2018
Agency for Toxic Substances and Disease Registry	Moiz Mumtaz, Ph.D.	Principal	Yes
Agency for Toxic Substances and Disease Registry	Edward Murray, Ph.D.	Other	Yes
National Cancer Institute	Myrtle Davis, D.V.M., Ph.D.	Principal	
National Cancer Institute	Ron Johnson, Ph.D.	Principal	Yes
National Cancer Institute	Chand Khanna, D.V.M., Ph.D.	Alternate	
National Cancer Institute	Mark Miller, Ph.D.	Alternate	Yes
National Institute for Occupational Safety and Health	Karen Heller Taylor, D.V.M.	Principal	Yes
National Institute of Environmental Health Sciences	Daniel Shaughnessy, Ph.D., D.A.B.T.	Principal	Yes
National Institute of Environmental Health Sciences	Nigel Walker, Ph.D., D.A.B.T.	Principal	
National Institute of Environmental Health Sciences	Richard Paules, Ph.D.	Alternate	Yes

Agency (Office)	**Representative**	**Representative Type (as of December 2017)**	**Service Continuing Into 2018**
National Institute of Environmental Health Sciences	Warren Casey, Ph.D., D.A.B.T.	Other	Yes
National Institute of Environmental Health Sciences	Nicole Kleinstreuer, Ph.D.	Other	Yes
National Institute of Environmental Health Sciences	Elizabeth Maull, Ph.D.	Other	Yes
National Institute of Standards and Technology	John Elliott, Ph.D.	Principal	Yes
National Institute of Standards and Technology	Elijah Petersen, Ph.D.	Alternate	Yes
National Institutes of Health	Christine Kelley, Ph.D.	Principal	Yes
National Institutes of Health	Harold Watson, Ph.D.	Alternate	Yes
National Library of Medicine	Pertti (Bert) Hakkinen, Ph.D.	Principal	Yes
National Library of Medicine	George Fonger	Alternate	Yes
National Library of Medicine	Jeanne Goshorn, M.S.	Alternate	Yes
Occupational Safety and Health Administration	Surender Ahir, Ph.D.	Principal	Yes
U.S. Consumer Product Safety Commission	Joanna Matheson, Ph.D.	Principal	Yes
U.S. Consumer Product Safety Commission	Kristina Hatlelid, Ph.D.	Alternate	Yes
U.S. Department of Agriculture	Carol Clarke, D.V.M., D.A.C.L.A.M.	Principal	Yes
U.S. Department of Agriculture	Kristina Adams, M.S.	Alternate	Yes
U.S. Department of Agriculture	Donna Malloy, D.V.M., D.A.C.L.A.M.	Alternate	

Agency (Office)	**Representative**	**Representative Type (as of December 2017)**	**Service Continuing Into 2018**
U.S. Department of Agriculture	Tim Allen	Other	
U.S. Department of Defense	Marla Brunell, D.V.M.., M.P.H., D.A.C.L.A.M., D.A.C.V.P.M.	Alternate	Yes
U.S. Department of Defense	Patrick Mason, Ph.D., S.E.S.	Principal	
U.S. Department of Defense	Dawn Fitzhugh, V.M.D., M.P.H.	Alternate	
U.S. Department of Defense	Emily N. Reinke, Ph.D., D.A.B.T.	Alternate (acting Principal since January 2017)	Yes
U.S. Department of Energy	Prem C. Srivastava, Ph.D.	Principal	Yes
U.S. Department of the Interior	Barnett A. Rattner, Ph.D.	Principal	Yes
U.S. Department of the Interior	Luke R. Iwanowicz, Ph.D.	Alternate	Yes
U.S. Department of the Interior	Tim Bargar, Ph.D.	Other	Yes
U.S. Department of the Interior	Adria Elkus, Ph.D.	Other	Yes
U.S. Department of the Interior	Paula F.P. Henry, Ph.D.	Other	Yes
U.S. Department of Transportation	Steve Hwang, Ph.D.	Principal	Yes
U.S. Department of Transportation	Ryan Vierling, Ph.D.	Alternate	Yes
U.S. Environmental Protection Agency (Office of Pesticide Programs)	Anna Lowit, Ph.D. (Co-chair)	Principal	Yes
U.S. Environmental Protection Agency (Office of Pollution Prevention and Toxics)	Louis (Gino) Scarano, Ph.D.	Other	Yes

Agency (Office)	**Representative**	**Representative Type (as of December 2017)**	**Service Continuing Into 2018**
U.S. Environmental Protection Agency (Office of Research and Development)	Pamela Noyes, Ph.D.	Alternate	Yes
U.S. Environmental Protection Agency (Office of Research and Development)	Stephanie Padilla, Ph.D.	Alternate	Yes
U.S. Environmental Protection Agency (Office of Research and Development)	Patience Browne, Ph.D.	Other	
U.S. Food and Drug Administration (Center for Biologics Evaluation and Research)	Ying Huang, Ph.D.	Other	
U.S. Food and Drug Administration (Center for Biologics Evaluation and Research)	Robin Levis, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Biologics Evaluation and Research)	Richard McFarland, Ph.D., M.D.	Other	
U.S. Food and Drug Administration (Center for Biologics Evaluation and Research)	Allen Wensky, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Devices and Radiological Health)	Simona Bancos, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Devices and Radiological Health)	Jennifer Goode	Alternate	Yes
U.S. Food and Drug Administration (Center for Devices and Radiological Health)	Vasant Malshet, Ph.D., D.A.B.T.	Other	
U.S. Food and Drug Administration (Center for	Rakhi Dalal-Panguluri, Ph.D.	Other	Yes

Agency (Office)	**Representative**	**Representative Type (as of December 2017)**	**Service Continuing Into 2018**
Devices and Radiological Health)			
U.S. Food and Drug Administration (Center for Drug Evaluation and Research)	Abigail C. Jacobs, Ph.D. (Co-chair through September 2017)	Principal	
U.S. Food and Drug Administration (Center for Drug Evaluation and Research)	Paul C. Brown, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Drug Evaluation and Research)	Jill Merrill, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Food Safety and Applied Nutrition)	Suzanne Fitzpatrick, Ph.D., D.A.B.T.	Principal	Yes
U.S. Food and Drug Administration (Center for Food Safety and Applied Nutrition)	Nakissa Sadrieh, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Tobacco Products)	Arianne Motter, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Center for Veterinary Medicine)	M. Cecilia Aguila, D.V.M.	Other	Yes
U.S. Food and Drug Administration (Center for Veterinary Medicine)	Li You, Ph.D.	Other	Yes
U.S. Food and Drug Administration (National Center for Toxicological Research)	Paul Howard, Ph.D.	Other	
U.S. Food and Drug Administration (National Center for Toxicological Research)	Donna Mendrick, Ph.D.	Other	Yes

Agency (Office)	Representative	Representative Type (as of December 2017)	Service Continuing Into 2018
U.S. Food and Drug Administration (National Center for Toxicological Research)	Mugimane (Manju) Manjanatha, Ph.D.	Other	Yes
U.S. Food and Drug Administration (Office of the Chief Scientist)	Tracy Chen, Ph.D., D.A.B.T.	Other	Yes
U.S. National Coordinator for OECD Test Guidelines Programme	Wanda Hall	Other	Yes

NICEATM and ICCVAM Publications, 2016-2017

NICEATM and ICCVAM Reports

ICCVAM. 2016. Biennial progress report 2014-2015: Interagency Coordinating Committee on the Validation of Alternative Methods [Internet]. Research Triangle Park (NC): National Institute of Environmental Health Sciences; [cited 14 March 2018]. Available from https://ntp.niehs.nih.gov/iccvamreport/2015/index.html.

Federal Register Notices

All *Federal Register* notices issued by NICEATM can be found on the NTP website at http://ntp.niehs.nih.gov/go/frn.

NIEHS. 2016. Interagency Coordinating Committee on the Validation of Alternative Methods; notice of public meeting; request for public input. Federal Register. 81(53):14865-14866.

NIEHS. 2016. Alternative approaches for acute inhalation toxicity to address global regulatory and non-regulatory data requirements; notice of webinars; registration information. Federal Register. 81(53):14864-14865.

NIEHS. 2016. Request for data and information on technologies used for identifying potential developmental toxicants. Federal Register. 81(126):42718-42719.

NIEHS. 2016. Request for data and information on technologies used to identify substances with the potential to cause acute systemic toxicity. Federal Register. 81(137):46696.

NIEHS. 2016. Scientific Advisory Committee on Alternative Toxicological Methods; announcement of meeting; request for comments. Federal Register. 81(161):55468-55469.

NIEHS. 2016. ICCVAM biennial progress report: 2014-2015; availability of report. Federal Register. 81(164):57926-57927.

NIEHS. 2016. Request for data and information on zebrafish embryo chemical screening. Federal Register. 81(213):76620-76621.

NIEHS. 2016. Using informatics to improve data analysis of chemical screening assays conducted in zebrafish; notice of webinars; registration information. Federal Register. 81(250):96024-96025.

NIEHS. 2016. Interagency Coordinating Committee on the Validation of Alternative Methods Communities of Practice webinar on incorporating chemical information: resources, limitations, and characterizing the domain of applicability for 21st century toxicity testing; notice of public webinar; registration information. Federal Register. 81(250):96025-96026.

NIEHS. 2017. ICCVAM notice of public meeting; request for public input. Federal Register. 82(78):19071-19073.

NIEHS. 2017. Scientific Advisory Committee on Alternative Toxicological Methods; announcement of meeting; request for comments. Federal Register. 82(168)161:37885-37887.

Journal Articles

Alves V, Capuzzi S, Muratov E, Braga R, Thornton T, Fourches D, Strickland J, Kleinstreuer N, Andrade C, Tropsha A. 2016. QSAR models of human data can enrich or replace LLNA testing for human skin sensitization. Green Chem. 18(24):6501-6515. https://doi.org/10.1039/C6GC01836J

Arciniega J, Wagner L, Prymula R, Sebo P, Isbrucker R, Descampe B, Chapsal JM, Costanzo A, Hendriksen C, Hoonaker M, Nelson S, Lidster K, Casey W, Allen D. 2016. Alternatives to HIST for acellular pertussis vaccines: progress and challenges in replacement. Report on an international workshop. Pharmeur Bio Sci Notes. 82-96.

Ball N, Cronin MTD, Shen J, Adenuga MD, Blackburn K, Booth ED, Bouhifd M, Donley E, Egnash L, Freeman JJ, Hastings C, Juberg DR, Kleensang A, Kleinstreuer N, Kroese ED, Lee AC, Luechtefeld T, Maertens A, Marty S, Naciff JM, Palmer J, Pamies D, Penman M, Richarz A-N, Russo DP, Stuard SB, Patlewicz G, van Ravenzwaay B, Wu S, Zhu H, Hartung T. 2016. Toward good read-across practice (GRAP) guidance. ALTEX. 33(2):149-166. https://doi.org/10.14573/altex.1601251

Bell SM, Chang X, Wambaugh JF, Allen DG, Bartels M, Brouwer KLR, Casey WM, Choksi N, Ferguson SS, Fraczkiewicz G, Jarabek AM, Ke A, Lumen A, Lynn SG, Paini A, Price PS, Ring C, Simon TW, Sipes N, Sprankle CS, Strickland J, Troutman J, Wetmore BA, Kleinstreuer NC. 2017. In vitro to in vivo extrapolation for high throughput prioritization and decision making. Toxicol In Vitro. 47:213-227. https://doi.org/10.1016/j.tiv.2017.11.016

Bell SM, Phillips J, Sedykh A, Tandon A, Sprankle C, Morefield SQ, Shapiro A, Allen D, Shah R, Maull EA, Casey WM, Kleinstreuer NC. 2017. An integrated chemical environment to support 21st century toxicology. Environ Health Perspect. 125(5):054501. https://doi.org/10.1289/EHP1759

Braga R, Alves V, Muratov E, Strickland J, Kleinstreuer N, Tropsha A, Andrade C. 2017. Pred-Skin: a fast and reliable web app to assess skin sensitization effect of chemicals. J Chem Inf Model. 57(5):1013-1017. https://doi.org/10.1021/acs.jcim.7b00194

Browne P, Noyes PD, Casey WM, Dix DJ. 2017. Application of adverse outcome pathways to U.S. EPA's Endocrine Disruptor Screening Program. Environ Health Perspect. 125(9):096001. https://doi.org/10.1289/EHP1304

Casati S, Aschberger K, Barroso J, Casey W, Delgado I, Kim TS, Kleinstreuer N, Kojima H, Lee JK, Lowit A, Park HK, Regimbald-Krnel MJ, Strickland J, Whelan M, Yang Y, Zuang V. 2017. Standardisation of defined approaches for skin sensitisation testing to support regulatory use and international adoption: position of the International Cooperation on Alternative Test Method. Arch Toxicol. 92:611-617. https://doi.org/10.1007/s00204-017-2097-4

Casey WM. 2016. Advances in the development and validation of test methods in the United States. Toxicol Res. 32:9-14. https://doi.org/10.5487/TR.2016.32.1.009

Clippinger AJ, Ahluwalia A, Allen D, Bonner JC, Casey W, Castranova V, David RM, Halappnavar

S, Hotchkiss JA, Jarabek AM, Maier M, Polk W, Rothen-Rutishauser B, Sayes CM, Sayre P, Sharma M, Stone V. 2016. Expert consensus on an in vitro approach to assess pulmonary fibrogenic potential of aerosolized nanomaterials. Arch Toxicol. 90(7):1769-1783. https://doi.org/10.1007/s00204-016-1717-8

Elliott JT, Rosslein M, Song NW, Toman B, Kinsner-Ovaskainen A, Maniratanachote R, Salit ML, Petersen EJ, Sequeira F, Lee J, Kim SJ, Rossi F, Hirsch C, Krug H F, Suchaoin W, Wick P. 2017. Toward achieving harmonization in a nano-cytotoxicity assay measurement through an interlaboratory comparison study. ALTEX. 34(2):201-218. https://doi.org/10.14573/altex.1605021

Ellis-Hutchings RG, Settivari RS, McCoy AT, Kleinstreuer N, Franzosa J, Knudsen TB, Carney EW. 2017. Embryonic vascular disruption adverse outcomes: linking high-throughput signaling signatures with functional consequences. Reprod Toxicol. 71:16-31. https://doi.org/10.1016/j.reprotox.2017.05.005

El-Masri H, Kleinstreuer N, Hines RN, Adams L, Tal T, Isaacs K, Wetmore B, Tan Y-M. 2016. Integration of life-stage physiologically based pharmacokinetic (PBPK) models with adverse outcome pathways (AOPs) and environmental exposure models to screen for environmental hazards. Toxicol Sci. 152(1):230-243. https://doi.org/10.1093/toxsci/kfw082

Grego S, Dougherty DR, Alexander FJ, Auerbach SS, Berridge BR, Bittner ML, Casey W, Cooley PC, Dash A, Ferguson SS, Fennell TR, Hawkins BT, Hickey AJ, Kleensang A, Liebman MN, Martin F, Maull EA, Paragas F, Qiao G, Ramaiahgari S, Sumner SJ, Yoon M. 2017. Systems biology for organotypic cell cultures. ALTEX. 34(2):301-310. https://doi.org/10.14573/altex.1608221

Griesinger C, Desprez B, Coecke S, Casey W, Zuang V. 2016. Validation of alternative in vitro methods to animal testing: concepts, challenges, processes and tools. Adv Exp Med Biol. 856:65-132. https://doi.org/10.1007/978-3-319-33826-2_4

Hamm J, Sullivan K, Clippinger AJ, Strickland J, Bell S, Bhhatarai B, Blaauboer B, Casey W, Dorman D, Forsby A, Garcia-Reyero N, Gehen S, Graepel R, Hotchkiss J, Lowit A, Matheson J, Reaves E, Scarano L, Sprankle C, Tunkel J, Wilson D, Xia M, Zhu H, Allen D. 2017. Alternative approaches for identifying acute systemic toxicity: moving from research to regulatory testing. Toxicol In Vitro. 41:245-259. https://doi.org/10.1016/j.tiv.2017.01.004

Hanna SK, Cooksey GA, Dong S, Nelson BC, Mao L, Elliott JT, Petersen EJ. 2016. Feasibility of using a standardized Caenorhabditis elegans toxicity test to assess nanomaterial toxicity. Environ Sci: Nano. 3:1080-1089. http://dx.doi.org/10.1039/C6EN00105J

Judson R, Houck K, Martin M, Richard AM, Knudsen TB, Shah I, Little S, Wambaugh J, Setzer RW, Kothiya P, Phuong J, Filer D, Smith D, Reif D, Rotroff D, Kleinstreuer N, Sipes N, Xia M, Huang R, Crofton K, Thomas RS. 2016. Analysis of the effects of cell stress and cytotoxicity on in vitro assay activity across a diverse chemical and assay space. Toxicol Sci. 152(2):323-339. https://doi.org/10.1093/toxsci/kfw092

Kleinstreuer NC, Ceger P, Allen DG, Strickland J, Chang X, Hamm JT, Casey WM. 2016. A curated database of rodent uterotrophic bioactivity. Environ Health Perspect. 124(5):556-562. https://doi.org/10.1289/ehp
Link to Web page with database

Kleinstreuer NC, Ceger P, Watt ED, Martin MT, Houck KA, Browne P, Thomas RS, Casey W, Dix D, Allen D, Sakamuru S, Xia M, Huang R, Judson RS. 2017. Development and validation of a computational model for androgen receptor activity. Chem Res Toxicol. 30(4):946-964. https://doi.org/10.1021/acs.chemrestox.6b00347

Kleinstreuer NC, Sullivan K, Allen D, Edwards S, Mendrick DL, Embry M, Matheson J, Rowlands

JC, Munn S, Maull E, Casey W. 2016. Adverse Outcome Pathways: From Research to Regulation scientific workshop report. Reg Toxicol Pharmacol. 76:39-50. https://doi.org/10.1016/j.yrtph.2016.01.007

Lillicrap A, Belanger S, Burden N, Pasquier DD, Embry MR, Halder M, Lampi MA, Lee L, Norberg-King T, Rattner BA, Schirmer K, Thomas P. 2016. Alternative approaches to vertebrate ecotoxicity tests in the 21st century: a review of developments over the last two decades and current status. Environ Toxicol Chem. 35:2637-2646. https://doi.org/10.1002/etc.3603

Lynch C, Sakamuru S, Huang R, Stavreva DA, Varticovski L, Hager GL, Judson RS, Houck KA, Kleinstreuer NC, Casey W, Paules RS, Simeonov A, Xia M. 2017. Identifying environmental chemicals as agonists of the androgen receptor by using a quantitative high-throughput screening platform. Toxicology. 385:48-58. https://doi.org/10.1016/j.tox.2017.05.001

Mansouri K, Abdelaziz A, Rybacka A, Roncaglioni A, Tropsha A, Varnek A, Zakharov A, Worth A, Richard AM, Grulke CM, Trisciuzzi D, Fourches D, Horvath D, Benfenati E, Muratov E, Wedebye EB, Grisoni F, Mangiatordi GF, Incisivo GM, Hong H, Ng HW, Tetko IV, Balabin I, Kancherla J, Shen J, Burton J, Nicklaus M, Cassotti M, Nikolov NG, Nicolotti O, Andersson PL, Zang Q, Politi R, Beger RD, Todeschini R, Huang R, Farag S, Rosenberg SA, Slavov S, Hu X, Judson RS. 2016. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. Environ Health Perspect. 124(7):1023-1033. https://doi.org/10.1289/ehp.1510267

Martin LA, Porter AG, Pelligrini VA, Schnatz PA, Jiang X, Kleinstreuer N, Hall JE, Verbiest S, Olmstead J, Fair R, Falorni A, Persani L, Rajkovic A, Mehta K, Nelson LM. 2017. A design thinking approach to primary ovarian insufficiency. Panminerva Med. 59(1):15-32. https://doi.org/10.23736/S0031-0808.16.03259-6

McCollum CW, de Vancells JC, Hans C, Vazquez-Chantada M, Kleinstreuer NC, Tal T, Knudsen T, Shah SS, Merchant FA, Finnell RH, Gustafsson J, Cabrera R, Bondesson M. 2017. Identification of vascular disruptor compounds by analysis in zebrafish embryos and mouse embryonic endothelial cells. Reprod Toxicol. 70:60-69. https://doi.org/10.1016/j.reprotox.2016.11.005

Mielke H, Strickland J, Jacobs MN, Mehta JM. 2017. Biometrical evaluation of the performance of the revised OECD Test Guideline 402 for assessing acute dermal toxicity. Regul Toxicol Pharmacol. 89:26-39. https://doi.org/10.1016/j.yrtph.2017.07.007

Miller MF, Goodson WH, Manjili MH, Kleinstreuer N, Bisson WH, Lowe L. 2017. Low-dose mixture hypothesis of carcinogenesis workshop: scientific underpinnings and research recommendations. Environ Health Perspect. 125(2):163-169. https://doi.org/10.1289/EHP411

Oki N, Leonard J, Nelms M, Bell S, Tan Y-M, Burgoon L, Edwards S. 2017. Linking environmental exposure to toxicity. In: Richardson RJ, Johnson DE, eds. Computational systems pharmacology and toxicology. Cambridge (UK): Royal Society of Chemistry. p. 60-88. https://doi.org/10.1039/9781782623731

Oki NO, Nelms MD, Bell SM, Mortensen HM, Edwards SW. 2016. Accelerating adverse outcome pathway development using publicly available data sources. Curr Environ Health Rep. 3(1):53-63. https://doi.org/10.1007/s40572-016-0079-y

Pamies D, Bal-Price A, Simeonov A, Tagle D, Allen D, Gerhold D, Yin D, Pistollato F, Inutsuka T, Sullivan K, Stacey G, Salem H, Leist M, Daneshian M, Vermuri MC, McFarland R, Coecke S, Fitzpatrick SC, Lakshmipathy U, Mack A, Wang WB, Daiju Y, Sekino Y, Kanda Y, Smirnova L, Hartung T. 2017. Good cell culture practice for stem cells and stem-cell-derived models. ALTEX. 34(1):95-132. https://doi.org/10.14573/altex.1607121

Planchart A, Mattingly CJ, Allen D, Ceger P, Casey W, Hinton D, Kanungo J, Kullman SW, Tal T,

Bondesson M, Burgess SM, Sullivan C, Kim C, Behl M, Padilla S, Reif DM, Tanguay RL, Hamm J. 2016. Advancing toxicology research using in vivo high throughput toxicology with small fish models. ALTEX. 33(4):435-452. https://doi.org/10.14573/altex.1601281
Recognized as an NIEHS Intramural Paper of the Month, September 2016

Polk WW, Sharma M, Sayes CM, Hotchkiss JA, Clippinger AJ. 2016. Aerosol generation and characterization of multi-walled carbon nanotubes exposed to cells cultured at the air-liquid interface. Part Fibre Toxicol. 13(1):20. https://doi.org/10.1186/s12989-016-0131-y

Russo DP, Kim MT, Wang W, Pinolini D, Shende S, Strickland J, Hartung T, Zhu H. 2017. CIIPro: a new read-across portal to fill data gaps using public large-scale chemical and biological data. Bioinformatics. 33(3):464-466. https://doi.org/10.1093/bioinformatics/btw640

Strickland J, Zang Q, Kleinstreuer N, Paris M, Lehmann DM, Choksi N, Matheson J, Jacobs A, Lowit A, Allen D, Casey W. 2016. Integrated decision strategies for skin sensitization hazard. J Appl Toxicol. 36(9):1150-1162. https://doi.org/10.1002/jat.3281
Recognized as an NIEHS Intramural Paper of the Month, October 2016

Strickland J, Zang Q, Paris M, Lehmann DM, Allen D, Choksi N, Matheson J, Jacobs A, Casey W, Kleinstreuer N. 2017. Multivariate models for prediction of human skin sensitization hazard. J Appl Toxicol. 37(3):347-360. https://doi.org/10.1002/jat.3366

Tal T, Kilty C, Smith A, LaLone C, Kennedy B, Tennant A, McCollum CW, Bondesson M, Knudsen T, Padilla S, Kleinstreuer NC. 2017. Screening for angiogenic inhibitors in zebrafish to evaluate a predictive model for developmental vascular toxicity. Reprod Toxicol. 70:70-81. https://doi.org/10.1016/j.reprotox.2016

Toman B, Rosslein M, Elliott JT, Petersen EJ. 2016. Estimation and uncertainty analysis of dose response in an inter-laboratory experiment. Metrologia 53:S40-S45. https://doi.org/10.1088/0026-1394/53/1/S40

Wagner L, Isbrucker R, Locht C, Arciniega J, Costanzo A, McFarland R, Oh H, Hoonakker M, Descamps J, Andersen SR, Gupta RK, Markey K, Chapsal JM, Lidster K, Casey W, Allen D. 2016. In search of acceptable alternatives to the murine histamine sensitsation test (HIST): what is possible and practical? Pharmeur Bio Sci Notes. 2016:151-170.

Zang Q, Mansouri K, Williams A, Judson R, Allen D, Casey W, Kleinstreuer N. 2017. In silico prediction of physicochemical properties of environmental chemicals using molecular fingerprints and machine learning. J Chem Inf Modeling. 57:(1)36-49. https://doi.org/10.1021/acs.jcim.6b00625
Recognized as an NIEHS Intramural Paper of the Month, April 2017

Zang Q, Paris M, Lehmann DM, Bell S, Kleinstreuer N, Allen D, Matheson J, Jacobs A, Casey W, Strickland J. 2017. Prediction of skin sensitization potency using machine learning approaches. J Appl Toxicol. 37(7):792-805. https://doi.org/10.1002/jat.3424

Zhu H, Bouhifd M, Kleinstreuer N, Kroese ED, Liu Z, Luechtefeld T, Pamies D, Shen J, Strauss V, Wu S, Hartung T. 2016. Supporting read-across using biological data. ALTEX. 33(2):167-182. https://doi.org/10.14573/altex.1601252

Abstracts

Adams K. 2017. Finding funding opportunities in 3Rs research [Abstract No. 792]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):171.

Allen D. 2016. Integrating alternative methods within a regulatory framework and the impact of AOPs in designing an integrated testing strategy to replace repeat exposure inhalation toxicity [Abstract No. 1705]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):165.

Allen D, Wilson D, Hotchkiss J, Morefield S, Casey W, Clippinger A. 2017. Integrating alternative approaches to replace animals in inhalation toxicity testing [Abstract No. 201]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):86.

Alzualde A, Alday A, Behl M, Tice RR, Paules R, Muriana A, Quevedo C. 2016. Toxicity profiling of flame retardants in zebrafish embryos using a battery of assays [Abstract No. 2456]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):344.

Auerbach SS, Phillips J, Svoboda DL, Yang L, Kuo B, Thomas RS, Yauk CL, Shah RR, Paules R. 2017. Evaluation of parameter settings in genomic benchmark dose analysis that minimize false discovery and maximize reproducibility [Abstract No. 2922]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):453.

Bell S, Burgoon L, Phillips J, Allen D, Casey W, Kleinstreuer N. 2017. A new tool for aligning assay endpoints to adverse outcome pathways [Abstract No. 207]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):155.

Bell S, Burgoon L, Phillips J, Ceger P, Allen D, Casey W, Kleinstreuer N. 2017. A new tool for aligning assay endpoints to adverse outcome pathways. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Bell S, Phillips J, Sedykh A, Sprankle C, Morefield S, Allen D, Casey W, Kleinstreuer N. 2017. An integrated chemical environment to support 21st century toxicology [Abstract No. 2935]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):456.

Bone A, Xia M, Sakamuru S, Huang R, Houtman R, van Beuningen R, Watt E, Kleinstreuer N, Judson R, Houck K. 2017. Identification of androgen receptor antagonists using Tox21 qHTS data and the MARCoNI assay [Abstract No. 1636]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):149.

Boyd WA, Pirone JR, Shaw MP, Kleinstreuer NC, Martin MT, Rashid A, Fostel JM, Thayer KA. 2017. Identification of environmental chemicals with potential roles in obesity and diabetes using animal studies from U.S. EPA and NTP toxicological databases [Abstract No. 3163]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):508.

Browne P. 2016. Screening chemicals for estrogen bioactivity using computational approaches [Abstract No. 1726b]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):170.

Cagle P, Padilla S, Tennant A, Tal T, Hedge J, Chorley B, Angrish M. 2017. An embryonic zebrafish screening model for early life-stage obesity [Abstract No. 2212]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):286.

Casey W. 2017. Funding research and validation of alternative methods in the United States [Abstract No. 806]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):171.

Casey W. 2017. A new strategic roadmap to establish new approaches for evaluating the safety of chemicals and medical products in the United States [Abstract No. 739]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):247.

Casey W. 2016. Strategy for implementing the vision of toxicity testing in the 21st century [Abstract]. Presented at the Fifth Annual Meeting of the American Society of Cellular and Computational Toxicology; Research Triangle Park, NC; 29-30 September 2016.

Casey W. 2017. Update from the U.S. Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) [Abstract No. 738]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):233.

Ceger P, Choksi N, Hamm J, Truax J, Daniel A, Allen D, Sutherland V, McIntyre B, Foster P, Maull E, Casey W. 2017. Development of a curated database of in vivo developmental toxicity data [Abstract No. 3159]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):507.

Chang X, Bell SM, Pirone JR, Allen D, Casey W, Kleinstreuer N. 2017. Open-source workflows for in vitro to in vivo extrapolation [Abstract No. 3185]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):513.

Chang X, Kleinstreuer N, Ceger P, Choksi N, Hsieh J-H, Wetmore BA, Ferguson S, DeVito MJ, Allen D, Casey W. 2016. In vitro to in vivo extrapolation for estrogenic activity of environmental chemicals [Abstract No. 2224]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):288.

Chang X, Pirone J, Bell SM, Allen D, Casey W, Kleinstreuer N. 2016. An open-source workflow for in vitro to in vivo extrapolation [Abstract]. Presented at the Fifth Annual Meeting of the American Society of Cellular and Computational Toxicology; Research Triangle Park, NC; 29-30 September 2016.

Chang X, Zang Q, Bell S, Allen D, Casey W, Kleinstreuer N. 2017. An open-source IVIVE workflow integrating QSAR and PK models [Abstract No. 203]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):197.

Chang X, Zang Q, Bell S, Allen D, Casey W, Kleinstreuer N. 2017. An open-source IVIVE workflow integrating QSAR and PK models [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Craig E, Perron M, Pope-Varsalona H, Lowit A. 2016. Implementation of the screening framework for cumulative risk assessment of pesticides [Abstract No. 2690]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):397.

Elespuru R, Pfuhler S, Aardema MJ, Chen T, Doak S, Doherty A, Farabaugh SC, Kenny J, Manjanatha M, Ouedraogo G, Mahadevan B, Moore MM, Stankowski LR, Tanir JY. 2017. Genotoxicity assessment of nanomaterials: best practices, assays, and methods [Abstract No. 2269]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):300.

Emond C, Ruiz P, Mumtaz M. 2016. Applications of the PBPK model of dioxins to evaluate real life exposure scenarios [Abstract No. 2227]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):289.

Fang H, Xu J, Liu Z, Liu Y, Harris S, Thakkar S, Zhou G, Zhang G, Howard P, Tong W. 2016. FDALabel database: a rich resource for study of pharmacogenomics biomarkers in advancing drug safety and precision medicine [Abstract No. 2750]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):411.

Ferguson S, Ramaiahgari SC, Rice J, Dunlap P, Smith-Roe S, Witt K, Auerbach S, Merrick A, DeVito M, Paules RS. 2017. Organotypic HepaRG cultures (384-well) and high throughput transcriptomics with 112 compounds to model human liver and characterize compound-induced biological-response "space" [Abstract No. 1590]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):139.

Fitzpatrick J, Karmaus AL, and Patlewicz G. 2017. Development of an acute oral toxicity dataset to facilitate assessment of existing QSARs and development of new models [Abstract]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017.

Fitzpatrick J, Karmaus AL, Pradeep P, Patlewicz G. 2017. Development of an acute oral toxicity dataset to facilitate assessment of existing QSARs and development of new models [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Fitzpatrick S. 2017. Advancing FDA regulatory science through innovation [Abstract No. 3124]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):499.

Fitzpatrick S. 2017. Advancing regulatory toxicology at the FDA [Abstract No. 805]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):73.

Fitzpatrick S. 2017. FDA CFSAN: modernizing approaches to regulatory toxicity testing [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Fitzpatrick S. 2017. Incorporating in vitro reproductive and developmental assays into regulatory risk assessment [Abstract No. 1611]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):143.

Fitzpatrick S. 2017. Low-dose non-monotonic responses [Abstract No. 2315]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):311.

Fitzpatrick S. 2017. Qualifying new in vitro tools for use in a regulatory risk assessment [Abstract No. 1614]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):144.

Hamm J, Ceger P, Boyles R, Reif D, Burgoon L, Haendel M, Walker N, Maull EA. 2017. Implementation of zebrafish ontologies for toxicology screening [Abstract No. 209]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):67.

Hamm J, Ceger P, Maull E, Padilla S, Perkins E, Planchart A, Stedman D, Tal T, Tanguay R, Volz D, Baker G, Stout M, Walker N. 2017. SEAZIT: the National Toxicology Program's Systematic

Evaluation of the Application of Zebrafish in Toxicology [Abstract No. 3161]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):507.

Hanna SK, Montoro Bustos AR, Peterson AW, Relpa V, Scanlan LD, Hosbas Coskun S, Cho TJ, Johnson ME, Hackley VA, Nelson BC, Winchester MR, Elliott JT, Petersen EJ. 2017. Positively charged nanoparticles lead to artifacts in a *Caenorhabditis elegans* toxicity assay [Abstract No. 1313]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):75.

Hedge JM, Jarema KA, Hunter DL, Padilla S. 2016. Strain-specific changes in locomotor behavior in larval zebrafish elicited by cholinergic challenge [Abstract No. 1795]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):186.

Houck K, Mosher S, Judson R, Wambaugh J, Martin M, Padilla S. 2016. Toxicity screening of a subset of the ToxCast Phase III chemical library using a zebrafish developmental assay [Abstract No. 1803]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):188.

Hsieh J-H, Huang R, Tice R, Paules R, Xia M, Auerbach S. 2016. Real-time cell viability profiling of Tox21 10K compounds [Abstract No. 1095]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):22.

Huppelschoten S, Niemeijer M, dem Hollander W, Baze A, Parmentier C, Paules R, Richert L, van de Water B. 2017. Gene expression profiling of primary human hepatocyte inter-individual variance in adaptive stress response activation [Abstract No. 2541b]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):363.

Jacobs A. 2016. CDER acceptance of alternative assays [Abstract No. 2574]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):370.

Jacobs A. 2017. International 3Rs efforts for pharmaceuticals and other products [Abstract No. 133]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):235.

Jaworska J, Natsch A, Ryan C, Strickland J, Ashikaga T, Miyazawa M. 2016. Bayesian integrated testing strategy (ITS) for skin sensitization potency assessment – a decision support system for quantitative weight of evidence and adaptive testing strategy [Abstract No. 2196]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):281.

Karmaus A, Allen D, Kleinstreuer N, Casey W. 2017. Characterizing variability across rat oral acute toxicity studies: implications for alternative model development [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Karmaus A, Allen D, Kleinstreuer N, Casey W. 2017. Characterizing the variability of LD50 values in acute toxicity studies: implications for alternative methods development [Abstract No. 205]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):221.

Klaric M, Alepee N, Allen D, Ashikaga T, Casey W, Clouet E, Cluzel M, Del Bufalo A, Gellatly N, Goebel C, Hoffmann S, Kern P, Kleinstreuer N, Kuehnl J, Mewes K, Miyazawa M, Petersohn K, Strickland J, Van Vliet E, Zang Q. 2017. Cosmetics Europe assessment of non-animal approaches for

predicting skin sensitization [Abstract No. 43]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):94.

Kleinstreuer N. 2017. In vitro insights into chemical carcinogenesis. [Abstract No. 802]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):64.

Kleinstreuer N. 2017. A strategy to ensure relevant science for regulatory acceptance and industry adoption. [Abstract No. 453]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):246.

Kleinstreuer N. 2017. Developmental toxicity potency of valproate analogues in a human pluripotent stem cell-based assay [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Kleinstreuer N. 2017. Pathway-based models to predict developmental and reproductive toxicologies. [Abstract No. 3074]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):489.

Kleinstreuer N. 2016. Skin sensitization testing strategy evaluation [Abstract No. 2533]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):361.

Kleinstreuer N, Ceger P, Allen D, Browne P, Houck K, Martin M, Thomas R, Dix D, Casey W, Judson R. 2016. Development and validation of a computational model for androgen receptor activity [Abstract]. Presented at the Fifth Annual Meeting of the American Society of Cellular and Computational Toxicology; Research Triangle Park, NC; 29-30 September 2016.

Kleinstreuer N, Ceger P, Browne P, Allen D, Hamm J, Casey W. 2016. Development and application of a reference database for androgen receptor activity [Abstract No. 2651]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):388.

Kleinstreuer N, Strickland J, Zuang V, Lowit A, Matheson J, Allen D, Casey W, Whelan M. 2017. Evaluating defined approaches to testing and assessment of skin sensitization potential [Abstract No. 3160]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):507.

Lowit A. 2017. EPA-OPPs initiative to modernize the acute “6-pack” [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Lowit A. 2017. Regulatory perspective: how do regulatory authorities currently utilize MOA data to make decisions about human relevancy? [Abstract No. 2728]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):143.

Lowit A, Schlosser C, Myska A, Patlewicz G, Paris M, Karmaus A, Strickland J, Allen D, Kleinstreuer N, Casey W. 2017. Replacing animals for acute systemic toxicity testing: a U.S. strategy and roadmap [Abstract No. 2182]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):279.

Lynch C, Sakamuru S, Huang R, Stavreva DA, Varticovski L, Hager GL, Judson RS, Houck KA, Kleinstreuer NC, Casey W, Paules RS, Xia M. 2017. Androgen receptor agonist identification and characterization by screening the Tox21 10K compound library [Abstract No. 1511]. Presented at the

56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):120.

Mansouri K, Kleinstreuer N, Watt E, Harris J, Judson R. 2017. CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity [Abstract No. 1389]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):93.

Martin WK, Padilla S, Kim YH, Hays MD, Hunter DL, Hazari MS, Gilmour MI, Farraj AK. 2017. Zebrafish locomotor responses predict irritant potential of smoke particulate matter from five biomass fuels [Abstract No. 2457]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):343.

Miller M, Goodson WH, Lowe L, Manjili MH, Kleinstreuer N, Bisson WH. 2017. Integrating the low-dose mixture hypothesis of carcinogenesis into the future of cancer research. [Abstract No. 1103]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):24.

Moser V, Padilla S. 2016. Esterase detoxification of acetylcholinesterase inhibitors by human liver samples in vitro [Abstract No. 2886]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):442.

Ono A, Watanabe S, Sugawara T, Wakabayashi K, Tahara Y, Horie N, Fujimoto K, Kusakari K, Kurokawa Y, Sozu T, Nakayama T, Kusao T, Kawakami T, Kojima K, Kojima H, Richmond J, Kleinstreuer N, Bae-Hwa K, Yamamoto Y, Fujita M, Kasahara T. 2017. Phase-1 of the validation study of amino acid derivative reactivity assay (ADRA): A novel in chemico alternative test methods of skin sensitization [Abstract No. 231]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):99.

Padilla S, Waalkes M, Hedge JM, Hunter DL, Jarema K. 2017. Comparison of the developmental and acute neurotoxicity of a library of organophosphorus pesticides using a vertebrate behavioral assay [Abstract No. 2641]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1) 386.

Palmer J, Smith A, Burrier R, Donley E, Kirchner F, Kroese D, Stober R, Kleinstreuer N. 2017. Developmental toxicity potency of valproate analogues in a human pluripotent stem cell-based assay [Abstract No. 631]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):46.

Pamies D, Bal-Price A, Coecke S, Allen D, Stacey G, Gstraunthaler G, Leist M, Hartung T. 2017. Good cell culture practice (GCCP 2.0) [Abstract No. 598]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):192.

Paris M, Strickland J, Allen D, Casey W. 2016. Retrospective analysis of acute toxicity tests for pesticides [Abstract No. 2990]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):467.

Paules R. 2017. Implementing approaches for moving Tox21 towards quantitative systems toxicology [Abstract No. 3114]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):497.

Paules R. 2017. The future of Tox21: changing the NTP landscape [Abstract No. 790]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):20.

Paules R, Hsieh J-H, Smith-Roe S, Witt KL. 2017. High-throughput approaches for characterizing

genotoxicity and carcinogenic potential: bridging classic and high-throughput approaches [Abstract No. 819]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):64.

Perron M, Lowit A, Smith C, Wilbur D. 2016. Development of a screening framework for pesticide cumulative risk assessment [Abstract No. 2689]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):397.

Quevedo C, Alzualke A, Alday A, Irjalba I, Holgado O, Muriana A, Ryan K, Paules R, Behl M. 2017. Toxicity profiling using a battery of assays in zebrafish embryos including teratogenicity, behavior, cardiotoxicity, ototoxicity, and hepatotoxicity [Abstract No. 2792]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):422.

Ramaiahgari SC, Walkyanatha S, Boyd W, DeVito MJ, Paules RS, Ferguson SS. 2016. Metabolically competent HepaRG spheroid model for in vitro toxicology studies [Abstract No. 2179]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):277.

Ramaiahgari SC, Walkyanatha S, Dixon D, DeVito MJ, Paules RS, Ferguson SS. 2017. High-dimensional toxicological assessment of chemical exposure on physiologically relevant 3D in vitro models [Abstract No. 1589]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):139.

Rowlands JC, Walker N. 2016. Bioactivity-based margin of exposure safety assessment: the next stop along the road to 21st century safety assessments [Abstract No. 1767a]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):179.

Scarano L. 2017. Progress report on development of the strategic plan to reduce, refine or replace use of vertebrate animal testing under the Lautenberg Act [Abstract]. Presented at the Sixth Annual Meeting of the American Society of Cellular and Computational Toxicology; Gaithersburg, MD; 21-22 September 2017.

Schnackenberg LK, Sun J, Breenhaw J, Bhattacharyya S, Gill P, Salminen WF, Mendrick DL, James LP, Beger RD. 2016. Translational biomarkers of acetaminophen-induced hepatotoxicity in urine samples [Abstract No. 1110]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):25.

Stevens J, DeMarini D, Hazari MS, Hunter DL, Padilla S, Farraj AK. 2016. Zebrafish locomotor responses demonstrate irritant effect of fine particulate matter sources and a role for TRPA1 [Abstract No. 2252]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):165.

Strickland J, Karmaus AL, Chang X, Paris M, Allen D, Kleinstreuer N, Casey W. 2017. Correlation of in vitro cytotoxicity and acute toxicity [Abstract No. 198]. Presented at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences; Seattle, WA; 20-24 August 2017. ALTEX Proceedings. 6(1):35.

Strickland J, Zang Q, Paris M, Lehmann DM, Bell S, Allen D, Matheson J, Jacobs A, Casey W, Kleinstreuer N. 2017. Prediction of skin sensitization potency using machine learning approaches [Abstract No. 2915]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):451.

Strickland J, Zang Q, Paris M, Lehmann DM, Bell S, Allen D, Matheson J, Jacobs A, Casey W, Kleinstreuer N. 2016. Prediction of skin sensitization potency using machine learning approaches

[Abstract]. Presented at the Fifth Annual Meeting of the American Society of Cellular and Computational Toxicology; Research Triangle Park, NC; 29-30 September 2016.

Strickland J, Zang Q, Paris M, Lehmann DM, Kleinstreuer N, Allen D, Choksi N, Matheson J, Jacobs A, Lowit A, Casey W. 2016. Multivariate models for prediction of human skin sensitization hazard [Abstract No. 2202]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):283.

Walker N. 2016. Biological canaries in the coal mine: strategic implications for utilizing bioactivity-based margins of exposure in human health risk assessment [Abstract No. 1767b]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):179.

Wilson VS, Conley J, Evans N, Cardon M, Rosenblum L, Iwanowicz LR, Hartig PC, Schenck K, Bradley PM. 2017. In vitro assessment of estrogen, androgen, and glutocorticoid bioactivity in a nationwide screen of United States stream waters [Abstract No. 1638]. Presented at the 56th Annual Meeting of the Society of Toxicology; Baltimore, MD; 12-16 March 2017. Toxicol Sci/Toxicologist. 156(1):149.

Yang C, Casey W, Choksi N, Ceger P, Kleinstreuer N, Allen D, Dharshan P, Bittner G. 2016. An in vitro test method for screening potential androgenic agonists and antagonists in MDA-kb2 cells [Abstract No. 3905]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):S176.

Yao J, Jones Y, Monroe W, Collins J, Howard P, Patri AK, Zhang Y. 2016. Size and crystal structure dependent inhibition of human mesenchymal stem cell adipogenic differentiation by nanoscale titanium dioxide [Abstract No. 2774]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):417.

Zang Q, Allen D, Casey W, Judson R, Kleinstreuer N. 2016. QSAR modeling to predict androgen receptor pathway activity [Abstract No. 1098]. Presented at the 55th Annual Meeting of the Society of Toxicology; New Orleans, LA; 13-17 March 2016. Toxicol Sci/Toxicologist. 150(1):23.

Articles in the NIEHS Environmental Factor Newsletter

Guidry V. September 2016. Research needed on low-dose mixtures and cancer. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/9/science-highlights/mixtures/index.htm

Hood E. November 2016. New initiative to modernize regulatory toxicity testing. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/11/science-highlights/testing/index.htm

Hood E. January 2017. Research collaborations take center stage at NTP board meeting. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2017/1/science-highlights/ntp/index.htm

Sprankle C. January 2016. Casey recognized for contributions to animal welfare. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/1/awards-recognition/animal-welfare/index.htm

Sprankle C. March 2016. Teratology Society recognizes Kleinstreuer. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/3/awards-recognition/kleinstreuer/index.htm

Sprankle C. June 2016. Kleinstreuer highlights groundbreaking approaches to safety testing. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from:

https://factor.niehs.nih.gov/2016/6/community-impact/kleinstreuer/index.htm

Sprankle C. July 2016. Plan to replace animal use shared at public forum. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/7/science-highlights/animal-use/index.htm

Sprankle C. November 2016. Experts address the challenge of inhalation toxicity testing. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/11/science-highlights/testing/index.htm

Sprankle C. December 2016. Kleinstreuer receives Lush Prize Young Researcher award. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2016/12/awards-recognition/kleinstreuer/index.htm

Sprankle C. March 2017. NIEHS grantee validates tissue chips for toxicity testing. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2017/3/science-highlights/tissuechip/index.htm

Sprankle C. June 2017. Public forum on alternatives to animal testing highlights next steps. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2017/6/science-highlights/testing/index.htm

Sprankle C. August 2017. New technologies highlighted at toxicology meeting. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2017/8/science-highlights/technologies/index.htm

Sprankle C. September 2017. International meeting highlights NTP efforts to replace animal tests. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2017/9/science-highlights/animal-testing/index.htm

Sprankle C. October 2017. Speeding the adoption of alternative safety tests. Environmental Factor [Internet]. [cited 15 Nov 2017] Available from: https://factor.niehs.nih.gov/2017/10/science-highlights/tests/index.htm

Sprankle C. December 2017. Scientists invited to build computer models that predict toxicity. Environmental Factor [Internet]. [cited 10 Jan 2018] Available from: https://factor.niehs.nih.gov/2017/12/science-highlights/tox-models/index.htm

Roster of SACATM Members 2016-2017

Name	Title	Company	Appointment End Year
Brian R. Berridge, D.V.M., Ph.D., D.A.C.V.P.	Director, Worldwide Animal Research Strategy	GlaxoSmithKline, King of Prussia, PA	2019*
Lauren E. Black, Ph.D.	Senior Scientific Advisor, Navigators Services	Charles River Laboratories, Reno, NV	2016
Michael B. Bolger, Ph.D.	Chief Scientist	Simulations Plus, Inc., Lancaster, CA	2020

Kelly P. Coleman, Ph.D., D.A.B.T., R.A.C.	Distinguished Scientist and Technical Fellow	Medtronic PLC, Minneapolis, MN	2020
Hisham K. Hamadeh, Ph.D., D.A.B.T., M.B.A.	Director, Comparative Biology and Safety Sciences	Amgen, Inc., Thousand Oaks, CA	2019
William P. Janzen	Executive Director of Lead Discovery	Epizyme, Inc., Cambridge, MA	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., D.A.B.V.T.	Senior Toxicologist and Senior Director of Toxicology Research	ASPCA Animal Poison Control Center, Urbana, IL	2016
Lawrence Milchak, Ph.D., D.A.B.T.	Senior Manager, Toxicology and Strategic Services	3M Corporation, St. Paul, MN	2019
Pamela Spencer, Ph.D., D.A.B.T.	Director of Regulatory and Product Stewardship	ANGUS Chemical Company, Buffalo Grove, IL	2019
Catherine E. Willett, Ph.D.	Director, Regulatory Toxicology, Risk Assessment, and Alternatives	The Humane Society of the United States, Gaithersburg, MD	2017
Clarlynda Williams-Devane, Ph.D.	Director, Bioinformatics, Genomics, and Computational Chemistry	North Carolina Central University, Durham, NC	2020
Wei Xu, Ph.D.	Associate Professor, Department of Oncology	McArdle Laboratory for Cancer Research, University of Wisconsin at Madison, Madison, WI	2017
Hao Zhu, Ph.D.	Assistant Professor, Department of Chemistry	Rutgers University, Camden, NJ	2019

*Berridge resigned from SACATM after being appointed NTP Associate Director in fall 2017.

Glossary 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.

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: 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.

Algorithm: a set of steps that are followed 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; the term new approach methodologies is also used and is becoming more prevalent.

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

Androgen receptor: 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.

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

Cardiomyocyte hypertrophy: increase in heart cell size, which can lead to abnormal enlargement or thickening of the heart muscle.

Cardiotoxicity: toxicity to the heart.

Cheminformatics: the application of computer and informational techniques in the field of chemistry, primarily methods for storage, indexing, and search of chemical information.

Chorion: in fish, the outermost membrane of an egg.

Co-cultures: cell culture systems that incorporate multiple cell types.

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

Countermeasure drugs: drugs developed to prevent or treat harm from a biological, chemical, radiological, or nuclear agent.

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

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

Defined approach: a testing strategy that consists of input data generated from identified methods and a data interpretation procedure, such as a machine learning model, flowchart, or decision tree, through which the data are evaluated.

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.

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: 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.

Extractables: substances that can be released from a medical device or material using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the conditions of clinical use.

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.

Hepatotoxicity: toxicity to the liver.

Hershberger assay: an assay conducted in castrated male rodents that measures the androgenic activity of a chemical by assessing the chemical's effect on the development of five male reproductive organs: ventral prostate, seminal vesicle, levator anibulbocavernosus muscle, Cowper's glands, and glans penis.

High-content screening: an approach that uses fluorescent tagging and automated imaging to assess changes in the structure and composition of individual cells in a high-throughput manner.

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.

Histopathology: the microscopic examination of tissue to identify and study the effects of injury or illness.

***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-cell 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.

Informatics: the science of processing data for storage and retrieval; information science.

Integrated approach 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 to indicate that specific additional tests are needed.

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

LC50: in traditional animal tests for acute inhalation or aquatic toxicity, the concentration that causes death in 50 percent of the animals tested; a value used to categorize toxic substances and determine the hazard phrases used on product labels.

LD50: in traditional animal tests for acute systemic oral or dermal toxicity, the dose that causes death in 50 percent 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.

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.

Microsampling: extraction of blood, plasma, or serum from experimental animals in quantities of 50 microliters or less; microsampling is generally less stressful for an animal and may allow reduction of animal use.

Microtiter plate: a flat plate with multiple wells used as small test tubes.

Mitochondrial dysfunction: reduction or loss of function of the mitochondria, energy-producing organelles, which can be caused by adverse drug reactions.

Murine local lymph node assay (LLNA): a widely used animal test to assess the potential for a chemical to cause allergic contact dermatitis.

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

Ontologies: standardized nomenclature systems**.**

Pharmacokinetics: an evaluation of the rate at which a chemical is absorbed, distributed, metabolized, and excreted once it enters the body, as a means to determine the relationship between exposure and toxicity (see also toxicokinetics).

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, whereas physiologically based models are usually multicompartment models with separate compartments corresponding to individual or combined organs that are interconnected by blood flows.

Phospholipidosis: accumulation of phosphate-fatty acid molecules within liver cells, often caused by certain types of drugs.

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 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.

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.

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 provides reproducible results over time and in different laboratories.

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

Reproductive toxicity: chemical effects on the reproductive system that interfere with an organism's sexual function or fertility.

Reverse toxicokinetics: an evaluation of the rate at which a chemical is absorbed, distributed, metabolized, and excreted once it enters the body. Used as a means to estimate the exposure level required to produce an internal dose equivalent to a concentration.

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.

Serogroup: a group of variants within a species of virus or bacteria having common cell surface antigens.

Six-pack studies: acute toxicity tests that generate data required by the EPA for pesticide registration. They include tests for acute systemic toxicity by the oral, dermal, and inhalation routes; skin and eye irritation; and skin sensitization.

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.

Steatosis: accumulation of fat droplets composed mostly of triglycerides within liver cells, which can be a sign of toxicity from alcohol or other chemicals.

Subchronic: Animal experiment designed to study effects produced by the test substance when administered either in repeated doses or continually in food, drinking-water, or air over a period of up to about 90 days.

Sublethal: a dose or concentration of a substance that is not high enough to cause death.

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.

Toxicokinetics: an evaluation of the rate at which a chemical is absorbed, distributed, metabolized, and excreted once it enters the body, as a means to determine the relationship between exposure and toxicity (see also pharmacokinetics).

Transactivation assay: an *in vitro* assay using cells containing a DNA plasmid that includes a regulatory sequence positioned upstream of the coding sequence of a reporter protein. Production of protein is proportional to stimulation of the regulatory sequence by a treatment chemical, and is often measured using light or color.

Up-and-down procedure: an acute systemic toxicity test that sequentially treats a small number of animals to provide an estimate of an LD50 or other toxicity metric.

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.

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.

Abbreviations and Acronyms

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)
ATSDR	Agency for Toxic Substances and Disease Registry
CaCVAM	Canadian Centre for the Validation of Alternative Methods
CDRH	Center for Devices and Radiological Health (U.S. Food and Drug Administration)
CPSC	U.S. Consumer Product Safety Commission
CSTP	Cellular Sentinels Toxicity Platform (U.S. Air Force)
CVB	Center for Veterinary Biologics (U.S. Department of Agriculture)
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
DPRA	Direct peptide reactivity assay
EASA	Electrophilic allergen screening assay
EPA	U.S. Environmental Protection Agency
EURL ECVAM	European Union Reference Laboratory for Alternatives to Animal Testing
FDA	U.S. Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FR	*Federal Register*
GHS	United Nations Globally Harmonized System of Classification and Labeling of Chemicals
h-CLAT	Human cell line activation test
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
LC50	In traditional acute inhalation or aquatic toxicity tests, the concentration that produces lethality in 50% of the animals tested
LD50	In traditional acute dermal or oral systemic toxicity tests, the dose that produces lethality in 50% of the animals tested
LLNA	Murine local lymph node assay
NCI	National Cancer Institute (National Institutes of Health)
NICEATM	National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences (National Institutes of Health)
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
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
QSAR	Quantitative structure-activity relationship
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SEAZIT	Systematic Evaluation of the Application of Zebrafish in Toxicology (National Toxicology Program)
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)
U.S.C.	United States Code
USAF	U.S. Air Force
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)