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A New Path Forward: The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

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In 2000, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was congressionally established, with representatives from Federal regulatory and research agencies that require, use, generate, or disseminate toxicologic and safety testing information. For over 15 y, ICCVAM and the National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) have worked together to promote the development, validation, and regulatory acceptance of test methods that replace, reduce, or refine the use of animals in regulatory testing. In 2013, both NICEATM and ICCVAM underwent major changes to their operating paradigms, to increase the speed and efficiency of regulatory approval and industry adoption of 3Rs testing methods within the United States and internationally. Accordingly, increased emphasis has been placed on international activities, primarily through interaction with the Organization for Economic Cooperation and Development and participation in the International Cooperation on Alternative Test Methods. In addition, ICCVAM has committed to increasing public awareness of and transparency about federal agencies' 3R activities and to fostering interactions with stakeholders. Finally, although it continues to support ICCVAM, NICEATM's work now includes validation support for Tox21, a collaboration aimed at identifying in vitro methods and computational approaches for testing chemicals to better understand and predict hazards to humans and the environment. The combination of more efficient operating paradigms, increased international collaboration, improved communication and interaction with stakeholders, and active participation in Tox21 likely will substantially increase the number of 3Rs methods developed and used in the United States and internationally.

Abbreviations: ICATM, International Cooperation on Alternative Test Methods; ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods; NICEATM, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods; NIEHS, National Institute of Environmental Health Sciences; NTP, National Toxicology Program; OECD, Organization for Economic Cooperation and Development.

Background Information on the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

In 2000, ICCVAM was formally established as permanent committee at the National Institute of Environmental Health Sciences (NIEHS) by the ICCVAM Authorization Act.[3] ICCVAM's mission is to facilitate the development, validation, and regulatory acceptance of new and revised regulatory test methods that replace, reduce, or refine the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.

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ICCVAM is composed of representatives from 15 United States federal regulatory and research agencies that require, use, or generate toxicologic and safety testing information. These organizations are the Agency for Toxic Substances and Disease Registry; Consumer Product Safety Commission; Departments of Agriculture, Defense, Energy, the Interior, and Transportation; Environmental Protection Agency; Food and Drug Administration; National Cancer Institute; National Institute for Occupational Safety and Health; National Institute of Environmental Health Sciences; NIH; National Library of Medicine; and Occupational Safety and Health Administration.

The Roles of ICCVAM in the Evaluation of Alternative Test Methods

Regulatory agencies in the United States are charged with protecting human and animal health and the environment. To this end, agencies must determine the hazards presented by substances such as pesticides, consumer products, cosmet-

ics, pharmaceuticals, and workplace chemicals. Testing these substances provides information about possible hazards and enables informed decisions regarding their responsible manufacture, use, storage, and disposal.

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

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

1. increase the efficiency and effectiveness of federal agency test method review;
2. eliminate unnecessary duplicative efforts and share experiences between federal regulatory agencies;
3. optimize the utilization of scientific expertise outside the federal government;
4. ensure that new and revised test methods are validated to meet the needs of federal agencies; and
5. replace, reduce, or refine the use of animals in testing, where feasible.[1]

The Authorization Act further delineates the following duties for ICCVAM:

1. coordinate the technical review and evaluation of new, revised, or alternative test methods;
2. foster interagency and international harmonization of test protocols that encourage replacing, reducing, or refining animal test methods;
3. assist with and provide guidance on validation criteria and processes;
4. submit ICCVAM test method recommendations to appropriate United States federal agencies;
5. consider requests from the public to review and evaluate new, revised, or alternative test methods that have evidence of scientific validity;
6. make ICCVAM's final test recommendations available to the public; and
7. prepare reports on ICCVAM's progress and accomplishments under the Act and make them available to the public every 2 y (ICCVAM Biennial Report).[1]

ICCVAM is a committee, not an organization or agency that has a dedicated staff, budget, and infrastructure. Instead, the National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), part of NIEHS, provides administrative and scientific support to ICCVAM. ICCVAM's efforts are supported by members of the respective agencies working together with NICEATM to accomplish specific goals, as described in the following sections.

2013: A New Vision and Direction for ICCVAM

During its first 15 y, ICCVAM evaluated alternative methods for regulatory use and made formal recommendations to federal agencies on a number of test methods. These methods are listed on the NTP website (http://ntp.niehs.nih.gov/go/regaccept). However, ICCVAM activities were not always driven by active engagement by the member agencies, and the development of ICCVAM products was not always sufficiently well-coordinated to maximize their acceptance and use. Consequently, ICCVAM stakeholders raised concerns that the methods recommended by ICCVAM were not always relevant to industry needs and were not being widely used for regulatory decision-making. Expectations for real reductions in animal use for toxicity testing were not being matched by documented progress.

In an *Environmental Health Perspectives* editorial,[1] NIEHS and NTP Director Linda Birnbaum announced that NIEHS would move forward with a different philosophy toward ICCVAM whereby the partner regulatory agencies would drive ICCVAM's activities. In addition, Dr Birnbaum sought to better align ICCVAM and NICEATM with the vision laid out by the National Academy of Sciences in the *2007 NRC Report on Toxicity Testing in the 21st Century*[2] as ICCVAM fulfilled its mission to implement the 3Rs of toxicity testing. Implementing the complete NRC vision will take time. Currently, ICCVAM and NICEATM are working together to improve the process and procedures to augment their efficiency and productivity.

In response to Dr Birnbaum's updated vision for ICCVAM, the committee developed the draft document titled *A New Vision and Direction for ICCVAM*.[4] The document presented ICCVAM's 1) areas of priority and scientific focus for immediate resource investment, 2) plans for improved communications with stakeholders and the public, and 3) interest in exploring new paradigms for the validation and utilization of alternative toxicologic methods. ICCVAM actively sought comment on the draft document from its advisory group, the Scientific Advisory Committee on Alternative Toxicology Methods, and the public and is carefully considering that input as it develops new operating procedures and plans upcoming activities.

Setting the Priorities and Areas of Scientific Focus for ICCVAM

As part of the new direction for ICCVAM, member agencies are taking a more active role in committee operations and priority setting. These changes will allow more effective resource investment in projects of interest and utility to the agencies. One aspect of these changes is a reorientation of resources invested by member agencies. A draft of the 2013–2017 5-year plan was released in 2012 and described numerous projects in which ICCVAM would participate, thus spreading its limited resources over many projects. ICCVAM is now considering an alternative strategy to identify priority areas for enhanced, immediate resource investment where there is an expectation of short-term success (that is, within the next 5 y). To maintain a high level of awareness of scientific advances in the key areas of relevance to ICCVAM, member agencies' representatives will play a prominent role in communicating needs specifically related to their agencies.

ICCVAM is developing revised procedures for the submission of new assays or projects and plans to share the revised procedures with the public for comment. A key change to the process is the need for documented support of the project by at least one federal agency. This federal agency will assume a sponsorship role for the proposed project, thereby ensuring that work done by ICCVAM is aligned with the needs of the agencies.

As noted earlier, ICCVAM has identified several projects where the scientific knowledge and technology has advanced substantially and where there is a reasonable likelihood of implementation into regulatory use within the next 5 y. As a result, ICCVAM and NICEATM plan to increase efforts on the following 3 key projects.

The US Department of Agriculture's Animal and Plant Health Inspection Service (USDA–APHIS) is committed to decreasing the number of hamsters used in *Leptospira* vaccine potency testing. The agency is actively seeking global acceptance of the

ELISA test it developed as an alternative and is exploring methods to reduce the numbers of animals used for back-titration and challenge strain development during the testing regimen.

In the realm of acute oral and dermal toxicity testing, ICCVAM's 2nd priority project, the US Environmental Protection Agency is evaluating the relative contribution of acute and dermal LD_{50} tests in providing information related to hazard labeling and the use of personal protective equipment. In addition, ICCVAM is investigating the utility of in vitro assays (for example, 3T3 NRU) for predicting oral LD_{50} values.

The 3rd priority area of ICCVAM for the next 5 years is skin sensitization. Great strides have been made in putting together a battery of in silico, in chemico, and in vitro tests for the assessment of skin sensitization. Such nonanimal alternative assays have been developed for the various key events in the adverse outcome pathway of skin sensitization. With support from the Environmental Protection Agency, Consumer Product Safety Commission, and Food and Drug Administration, ICCVAM has announced the development of a plan for the evaluation of alternative skin sensitization test methods and testing strategies. Activities proposed as part of the plan include collaboration with international partners to support ongoing development and validation of in vitro skin sensitization test methods; evaluation of alternative test method and testing strategy submissions for skin sensitization; and promotion of validated methods through workshops, webinars, and guidance documents. The newly established ICCVAM Skin Sensitization Working Group is reviewing and evaluating the public's response to the plan and will advance recommendations for appropriate ICCVAM activities for the next several years. More information about the ICCVAM plan to evaluate alternative skin sensitization test methods can be obtained on the NTP website (http://ntp.niehs.nih.gov/go/40498).

The identification of the described priority areas does not mean that ICCVAM will no longer engage in following the scientific advancement of other alternative approaches. On the contrary, ICCVAM is improving its coordination with ongoing international activities on alternatives, and agency representatives will regularly update ICCVAM on their agencies' activities. As other promising alternative approaches are developed, ICCVAM will change its priorities to maximize potential progress toward implementing the 3Rs. For example, as described regarding alternatives for skin sensitization tests, ICCVAM's historic focus on the one-to-one replacement of an in vivo test with an alternative assay is changing. In the future, more complex batteries of tests that evaluate systemic toxicity will need to be assembled. As a consequence, ICCVAM will place less emphasis on replacement of in vivo toxicity endpoints with a single alternative assay and more emphasis on assembling batteries of assays and including in silico approaches to interpret and analyze data from such batteries.

Improved Communication with Stakeholders and the Public

One of the roles of ICCVAM is to promote the acceptance and implementation of validated and accepted alternative toxicologic methods that replace, reduce, or refine animal use. To accomplish this role, ICCVAM needs to communicate better the efforts by federal agencies toward promoting implementation of the 3Rs and their acceptance by both regulators and the regulated community. To this end, ICCVAM has committed to improving agency-specific 3Rs content on the ICCVAM website. ICCVAM plans to use its website as a single repository for highlighting and increasing the transparency of all current and past activities and accomplishments. Many of these 3Rs activities are directed toward improving and fundamentally changing regulatory toxicity testing. The website will now include information about well-known activities such as the Environmental Protection Agency's ToxCast and the NIH's Tox21 projects as well as others that are less publicized. In addition, changes are being made to the website for easier navigation.

As another means to improve communication, ICCVAM will engage broadly with the scientific community and stakeholders to advance regulatory science and encourage wider application of alternative methods in regulatory decision-making. ICCVAM plans to increase interactions with stakeholders (for example, regulated community and public interest groups) though a variety of mechanisms such as focused workshops with well-defined objectives, community of practice webinars, and web-based comment forms. In addition, ICCVAM will foster interactions with stakeholders via face-to-face forums that will facilitate the direct communication of ideas and suggestions and exchange of information.

To increase federal agencies' awareness of international 3Rs efforts, ICCVAM has made the Untied States national coordinator for the Organization for Economic Cooperation and Development (OECD) an ad hoc member. The national coordinator provides ICCVAM updates on topics of interest to federal agencies and uses the committee as a forum for obtaining feedback on those activities for OECD. In addition, this direct interaction increases agencies' awareness of OECD 3Rs projects and fosters their participation in them.

Focus and Goals of OECD

OECD's health-effects test guidelines represent internationally agreed-upon methods that can be used by government, industry, and independent laboratories in the 34 OECD member countries to determine the safety of chemicals and chemical preparations. The OECD Adverse Outcome Pathway Development Program represents a key resource to support development and utilization of new in vitro test methods. Adverse outcome pathways are the central element of a toxicologic knowledge framework being developed by OECD member countries to support chemical risk assessment based on mechanistic reasoning. The ability to use these pathways for informed decision-making is dependent on our ability to effectively use data from different 'steps' of the pathway, a process referred to as Integrated Approaches to Testing and Assessment. ICCVAM, NICEATM, and their international partners are actively involved in developing integrated approaches that increase our ability to accurately assess the safety of chemicals as they decrease our reliance on animal models for toxicity testing.

The International Cooperation on Alternative Test Methods (ICATM)

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: 1) ensure the optimal design and conduct of validation studies; 2) ensure high-quality independent scientific peer reviews of alternative test methods; 3) ensure consistent and transparent stakeholder involvement; 4) achieve greater efficiency and effectiveness by internationally leveraging limited resources and avoiding duplication of effort; and

5) 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. In addition to ICCVAM, the current ICATM partner organizations are The European Union Reference Laboratory for Alternatives to Animal Testing (EURL_ECVAM); The Japanese Center for the Validation of Alternative Methods (JaCVAM); Health Canada's Environmental Health Science and Research Bureau; and The Korean Center for the Validation of Alternative Methods (KoCVAM).

ICATM coordination meetings occur several times each year and provide an opportunity for the 5 organizations to discuss activities in the major areas of cooperation. Regular interactions allow the ICATM partners to develop strong communication and working relationships in support of collaborative test method development.

New Paradigms for Validation

Considerable worldwide interest exists in developing an understanding of how biologic pathways become engaged in toxicity responses. The intent is that knowledge about these pathways would lead to the development of predictive, integrated testing strategies that likely would combine in silico approaches and multiple in vitro or high-throughput assays with limited, targeted testing in laboratory animals. There are various statistical approaches to assembling components of a 'most predictive' test battery as well as different statistical models for integrating all relevant information and assay results. Both the batteries and models as alternative methods may warrant consideration by ICCVAM. In addition, numerous efforts are underway to develop in silico and in vitro approaches for screening and prioritization of chemicals for testing. Ultimately, the application of these alternative methods may differ (regulatory testing for safety evaluation or risk assessment compared with screening or prioritization), and as such, the concept of validation in the context of use needs to be reconsidered. ICCVAM intends to engage the public in discussions about the concept of validation and its role in this new paradigm.

In addition to changing the concept of validation, ICCVAM agencies recognize that reevaluating standing policy in response to new data could substantially affect the number of animals used for regulatory safety testing.

Background Information on NICEATM

NICEATM is an office of the Division of the NTP at NIEHS, one of the organizations within NIH. Historically, NICEATM's responsibilities have focused on providing scientific and operational support for ICCVAM activities; conducting and publishing analyses and evaluations of data from new alternative testing approaches; and providing information to test method developers, regulators, and regulated industry and organizing workshops and symposia on topics of interest.

Supporting Tox21, a New Role for NICEATM

Tox21 is a multiagency collaboration that includes NIEHS–NTP, the NIH's National Center for Advancing Translational Sciences, the Environmental Protection Agency's National Center for Computational Toxicology, and the Food and Drug Administration. The objective of this partnership is to shift the assessment of chemical hazards away from traditional laboratory animal toxicology studies to an evaluation based on target-specific, mechanism-based, biologic observations largely obtained by using in vitro assays, with the ultimate aim of improving risk assessment for humans and the environment. Tox21's strategy is to use in vitro high-throughput and high-content screening technologies to test a broad variety of approximately 10,000 substances and consider data from those screens collectively to assess effects on biologic pathways related to toxicity. Data from Tox21 testing will be used to develop a better understanding of these toxicity or 'adverse outcome' pathways, ideally enabling the eventual use of in vitro assay data to predict the adverse effects of chemical exposures in vivo. More information about Tox21 can be found on the NTP website (http://ntp.niehs.nih.gov/go/tox21).

Beginning in 2013, NICEATM expanded its activities beyond ICCVAM. In her *Environmental Health Perspectives* editorial,[1] NIEHS and NTP Director Linda Birnbaum enlarged the scope of NICEATM to include providing bioinformatic and computational toxicology support to the interagency Tox21 effort. The intent was to position NICEATM in a bridging role between regulators and Tox21, thereby focusing on the validation of Tox21 methods for regulatory use and strengthening activities related to the 3Rs.

Summary and Conclusions

ICCVAM and NICEATM recently chartered a new path forward that is largely based on changing their operating paradigms to be more productive, more responsive to stakeholders, and more engaged internationally. These organizations are working together to promote more efficient approaches to develop and validate methods that employ the 3Rs, and they are exploring options that would allow these methods to be expeditiously accepted by regulators and used by stakeholders. ICCVAM recognizes the need for international coordination if 3R methods are going to be used to their maximal potential and has placed increased emphasis on interactions with OECD and through ICATM, an alliance of validation organizations from the United States, Europe, Japan, Korea, and Canada. NICEATM's roles have expanded to include providing support for the Tox21 initiative, an interagency collaboration that uses high-throughput screening and other advanced approaches to better understand and predict chemical hazards to humans and the environment. The combination of more efficient operating paradigms, increased international collaboration, improved interaction with stakeholders, and the evaluation of Tox21 data is anticipated to substantially increase the number of 3R methods developed and used in the United States and internationally.

Acknowledgement

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