



News from NICEATM and ICCVAM

We are pleased to provide this update on recent and planned activities of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and its Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM is an interagency committee composed of representatives from 15 U.S. Federal regulatory and research agencies that require, use, or generate toxicological and safety testing information. ICCVAM is charged by law with evaluating the usefulness and limitations of new, revised, and alternative safety testing methods with regulatory applicability and providing recommendations on their scientific validity to U.S. Federal agencies. The agencies must respond to ICCVAM within 180 days. ICCVAM promotes the scientific validation and regulatory acceptance of safety testing methods that more accurately assess the health hazards of chemicals and products while reducing, refining (decreasing or eliminating pain and distress), and replacing animal use.

NICEATM administers ICCVAM and provides scientific and operational support for ICCVAM-related activities. Consistent with the NTP mission, NICEATM also conducts and coordinates international validation studies on high priority improved safety testing methods and strategies. NICEATM and ICCVAM collaborate to evaluate new and improved test methods and strategies applicable to the needs of U.S. Federal agencies and to achieve national and international harmonization of safety testing methods.

NTP Director signs international agreement at Society of Toxicology Annual Meeting

Dr. Linda Birnbaum, Director of NTP and the National Institute of Environmental Health Sciences (NIEHS), joined international counterparts last month in signing an agreement that expands cooperation to reduce the number of animals required for safety testing worldwide. The agreement brings a new country, the Republic of Korea, into an existing effort to promote international cooperation that should permit more rapid acceptance of new safety testing methods for chemicals and products. New testing methods can better protect public health and also reduce the number of animals needed for safety testing.

The agreement, a modification to the April 2009 International Cooperation on Alternative Test Methods (ICATM), was signed in a ceremony on March 8 during the 50th Annual Meeting of the Society of Toxicology (SOT) in Washington, DC, USA. Dr. Birnbaum signed as the U.S. representative on behalf of NICEATM, one of the national organizations participating in the agreement. Other attendees at the ceremony included Dr. Joachim Kreysa of the European Centre for the Validation of Alternative Methods (ECVAM), Dr. Yasuo Ohno of the Japanese National Institute of Health Sciences, Mr. Michael Inskip of Health Canada, and Dr. Seung Hee Kim of the Korean Food and Drug Administration.

The ICATM agreement will promote international cooperation on the scien-

tific validation of new test methods. Test methods that are shown to be sufficiently accurate and reproducible based on strong scientific information will be more readily accepted by regulatory agencies worldwide. This, in turn, will lead to broader acceptance and use of these methods, benefiting both public health and animal welfare.

More information on the ICATM agreement is available on the NICEATM-ICCVAM web site at: <http://iccvam.niehs.nih.gov/about/icatm.htm>

SOT informational session on the International Cooperation on Alternative Test Methods (ICATM)

NICEATM Director Dr. William Stokes co-chaired an information session on ICATM at the SOT Annual Meeting. The goal of the session, attended by about 100 people, was to inform SOT members of the important role of ICATM in facilitating the rapid international adoption of newly validated alternative safety testing methods. In addition to chairing the session, Dr. Stokes gave an introductory presentation that described the purposes and goals of ICATM. His presentation also outlined the validation process for new test methods and noted the contribution of the ICATM collaboration to the adoption of several international guidelines for chemical safety testing in 2009 and 2010.

The information session also included updates on recent ICATM contributions



and future plans by each of the ICATM participating organizations. Dr. Kreysa and Mr. Inskip provided updates from ECVAM and Health Canada, while former ICCVAM Chair Dr. Marilyn Wind and Dr. Hajime Kojima of the Japanese Center provided updates on U.S. and Japanese activities for the Validation of Alternative Methods, respectively. Dr. Soon Young Han, director of the Korean Center for the Validation of Alternative Methods, gave a summary of recent activities in the Republic of Korea.

Presentations from the SOT session on ICATM and information on all NICEATM-ICCVAM activities at the 2011 SOT Annual Meeting can be found on the NICEATM-ICCVAM web site at: <http://iccvam.niehs.nih.gov/meetings/SOT11/sotablst.htm>

U.S. Federal agencies accept ICCVAM recommendations for new test methods to identify ocular toxicity hazards

U.S. Federal regulatory and research member agencies of ICCVAM have endorsed ICCVAM recommendations on the usefulness and limitations of new alternative ocular safety testing methods. The recommended test methods serve to replace animal use for some eye safety testing and to provide for pain-free testing when it is necessary to use animals to confirm whether chemicals and products may cause eye injuries.

ICCVAM developed these recommendations following a comprehensive evaluation of the scientific validity of the proposed test methods and approaches, which included independent scientific peer review by a panel of international experts at a public meeting. Acceptance of these recommendations by regulators is expected to result in the use of fewer animals for eye safety testing as well as the elimination of discomfort for those animals that still are required for testing according to U.S. Federal regulations.

In response to requests from the U.S. Environmental Protection Agency, NICEATM and ICCVAM evaluated several *in vitro* test methods proposed for classifying ocular hazards without the use

of live animals. ICCVAM recommended one of these methods, the Cytosensor microphysiometer (CM) test method, as a screening test to identify some types of substances that will not cause sufficient injury to require eye hazard labeling. The CM test method is the first *in vitro* eye safety testing adopted for use in what is referred to as a “bottom-up approach” to testing. ICCVAM also recommended that the CM test method could be used to identify some types of substances that may cause permanent or severe eye injuries.

ICCVAM evaluated several other *in vitro* test methods and testing strategies but concluded that their ability to predict ocular hazard potential needs to be improved before they may be used for the specific regulatory safety testing applications under consideration. Accordingly, ICCVAM made recommendations on future studies that could potentially improve these test methods and testing strategies.

ICCVAM recommended that pain management procedures always be used when it is necessary to use animals for ocular safety testing. The procedures include the routine use of topical anesthetics similar to those used for human eye surgeries as well as systemic analgesics. The procedures also include specific clinical signs and lesions that, if observed during the animal study, can be used as humane endpoints to terminate the study early.

The ICCVAM recommendations form the basis for proposals being considered this year to update the existing OECD test guideline on ocular safety testing and a proposed new test guideline for the CM test method.

Protocols for the CM test method, the pain management procedure for *in vivo* testing, and other ICCVAM-recommended test methods are available on the test method protocols page of the NICEATM-ICCVAM web site at: <http://iccvam.niehs.nih.gov/methods/protocols.htm>. Additional information on the September 2010 ICCVAM recommendations on ocular safety testing methods and approaches can be found on the NICEATM-ICCVAM web site at: <http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm>

ICCVAM recommendations on ocular safety testing methods and approaches were presented at a January 2011 workshop on “Best Practices for Regulatory Safety Testing.” Materials from this workshop are available on the NICEATM-ICCVAM web site at <http://iccvam.niehs.nih.gov/meetings/Implement-2011/ImplmntWksp.htm>. These include the workshop presentations, links to an archived webcast of the plenary session of the workshop, workshop agenda, abstracts of poster session presentations, and background information.

ICCVAM peer panel reviews *in vitro* test method for identification of potential endocrine disruptor activity

In a public meeting on March 29-30, 2011 at the National Institutes of Health, an independent international peer review panel agreed with ICCVAM draft test method recommendations stating that an *in vitro* test method may be used as an initial screen to identify substances with the potential to enhance or inhibit activation of the estrogen receptor. More than 40 scientists representing industry, academia, and U.S. Federal regulatory agencies attended the peer panel meeting, which was open to the public.

NICEATM convened the peer review panel meeting as part of the ICCVAM test method evaluation process. The panel, which included expert scientists from seven countries, reviewed data from a NICEATM-sponsored validation study to assess the accuracy and reliability of an *in vitro* estrogen receptor (ER) transcriptional activation (TA) test method. This test method, the BG1Luc ER TA, was considered for qualitative identification of substances with *in vitro* ER agonist or antagonist activity. The BG1Luc ER TA test method uses human ovarian cancer cells to measure whether and to what extent a substance induces or inhibits TA activity via an ER-mediated pathway.

Endocrine disruptors are substances that interfere with the normal function of hormones in the endocrine system. These interferences can lead to abnormal growth, development, or reproduction. Studies in-



dicating that animal populations exposed to high levels of these substances have an increased incidence of reproductive and developmental abnormalities have raised concerns about the potential human health effects of these substances.

To comply with new Federal laws addressing the health effects of endocrine disruptors, the U.S. Environmental Protection Agency implemented an Endocrine Disruptor Screening Program to assess pesticides and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife. The BG1Luc ER TA test method may be appropriate for use as an initial screen in the EDSP.

A report of the peer review panel meeting containing a detailed summary of the panel's discussions and conclusions will be published in May and will be available on the NICEATM-ICCVAM web site at: <http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm>

Save the date: International Workshop on New Approaches to Rabies Vaccine Potency Testing: State of the science and the way forward

A recent international workshop organized by NICEATM, ICCVAM, and its international partners identified rabies vaccines as one of the three highest priorities for future research, development, and validation of alternative test methods that could further refine, reduce, and ultimately replace animal use for potency and safety testing. Based on recent scientific and technological advances, several alternative approaches have been proposed or are currently available. NICEATM and ICCVAM will convene an International Workshop on New Approaches to Ra-

bies Vaccine Potency Testing on October 11-13, 2011, at the US Department of Agriculture Center for Veterinary Biologics in Ames, Iowa. The workshop will bring together international scientific experts from government, industry, and academia to review the available methods and approaches and to define efforts necessary to achieve global acceptance and implementation. Registration information and a workshop program will be available on the NICEATM-ICCVAM website at: <http://iccvam.niehs.nih.gov/meetings/schedule.htm>

NICEATM-ICCVAM requests nominations and submissions of test methods with potential regulatory applications

NICEATM and ICCVAM welcome nominations and submissions from the public for new or revised alternative safety testing methods with the potential to improve the accuracy of safety assessments and the potential to reduce, refine, or replace the use of animals. Test methods that incorporate advances in science and technology are especially encouraged.

- *Nominations* can be submitted for proposed test method validation studies, specific test method or validation issues, or requests for test method evaluations. Such nominations are typically addressed with international validation studies, workshops, conferences, or test method independent scientific peer review meetings.
- When validation studies that adequately characterize a test method's usefulness and limitations for a specific proposed regulatory requirement or application have been completed, a *submission* can be sent to ICCVAM for review and technical evaluation of the test method.

ICCVAM then develops a test method evaluation report and formal recommendations that are forwarded to U.S. Federal agencies for acceptance consideration.

Organizations or individuals that wish to propose nominations or submissions of promising test methods are encouraged to contact NICEATM for information and guidance on preparing proposals. Submission and nomination guidelines also are available on the NICEATM-ICCVAM website at <http://iccvam.niehs.nih.gov/SuppDocs/submission.htm>

For More Information

Questions about NICEATM and ICCVAM activities are welcomed and can be directed to Dr. William S. Stokes, Director, NICEATM, at niceatm@niehs.nih.gov; phone +1 919 541 2384; fax +1 919 541 0947. Copies of documents mentioned in this update also can be obtained by contacting NICEATM.

Information on the availability of NICEATM and ICCVAM draft documents, requests for nominations of experts to participate at workshops and on peer review panels, and specific information about NICEATM-ICCVAM meetings are communicated via the ICCVAM-all e-mail list and in notices posted in the U.S. *Federal Register*.

Subscribers to the ICCVAM-all e-mail list are notified directly of NICEATM-ICCVAM activities. Subscribers receive e-mail notification of NICEATM-ICCVAM Federal Register notices, availability of NICEATM-ICCVAM reports, notices of upcoming meetings, requests for public comments or data, and other events of interest to our stakeholders. If you would like to subscribe to the ICCVAM-all list, or for more information, please visit the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/contact/ni_list.htm