



## 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 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, which 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 work to achieve national and international harmonization of safety testing methods.

### **ICCVAM recommends alternative method to identify chemicals and products with significant potential to cause allergic contact dermatitis**

ICCVAM recently forwarded recommendations for using the murine local lymph node assay, or LLNA, to categorize the potency of some chemicals that cause allergic contact dermatitis in humans as strong sensitizers. Strong sensitizers are those substances considered to have a significant potential for causing skin hypersensitivity resulting in allergic contact dermatitis.

ICCVAM concluded that the LLNA could correctly categorize some substances as strong sensitizers using a criterion published in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). However, nearly half of the known human strong sensitizers evaluated by ICCVAM were not identified using the GHS criterion. ICCVAM concluded that additional information would need to be considered to confirm whether substances that do not meet this criterion are or are not strong sensitizers. The recommendations are based on a comprehensive test method evaluation by ICCVAM and NICEATM, and were announced July 28 in the *Federal Register*.

Substances with the potential to cause ACD can also be categorized with traditional test methods using guinea pigs. However, the LLNA uses fewer animals than guinea pig test methods, requires less time to perform, provides dose-response information, and, in most cases, eliminates the potential for pain and distress in the test animal. In accordance with the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals, the LLNA should be routinely considered when planning animal studies to evaluate whether chemicals and products are strong sensitizers in order to minimize animal use and to avoid pain and distress.

The ICCVAM report including the recommendations has been transmitted to U.S. Federal agencies for their review and response. A summary of the ICCVAM recommendations and a link to the report are available on the NICEATM-ICCVAM website at <http://iccvam.niehs.nih.gov/methods/immunotox/LLNAspotency.htm>. Responses from Federal agencies will be available by early 2012 and will be posted on this page as they are received.

NICEATM and ICCVAM are also currently evaluating several *in vitro* and *in chemico* methods for their potential to further reduce and eventually replace animal use for ACD safety testing. Information on NICEATM and ICCVAM evaluations of methods for ACD safety testing can be found at: <http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm>



### **ICCVAM proposes procedures to reduce animal use for eye safety testing**

ICCVAM is proposing eye hazard classification criteria that will provide the same or greater level of eye hazard classification as current U.S. Federal Hazardous Substances Act (FHSA) regulations, while using 50% to 83% fewer animals. The draft recommendations are based on an analysis conducted in collaboration with NICEATM. A manuscript describing the NICEATM analysis was recently published in the journal *Regulatory Toxicology and Pharmacology* (Haseman et al., *Regul. Toxicol. Pharmacol.* 61, 98-104).

NICEATM announced availability of the draft recommendations and requested public comment via a *Federal Register* notice published August 12. ICCVAM will consider all public comments and comments made by its advisory committee when finalizing its recommendations. Final ICCVAM recommendations will be made available on the NICEATM-ICCVAM website and forwarded to relevant Federal agencies for their consideration.

Links to the ICCVAM draft recommendations, the *Regulatory Toxicology and Pharmacology* article, and other information about the NICEATM analysis may be found on the NICEATM-ICCVAM website at: <http://iccvam.niehs.nih.gov/methods/ocutox/reducenum.htm>

### **ICCVAM Advisory Committee meets**

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on June 16 and 17. SACATM is composed of representatives of regulated industries and other ICCVAM stakeholders. It advises the Director of the National Institute of Environmental Health Sciences (NIEHS), ICCVAM, and NICEATM about Federally mandated ICCVAM functions and ICCVAM activities.

At the June meeting, SACATM was provided with an overview of NICEATM and ICCVAM activities and accomplish-

ments over the past year. SACATM also received a detailed summary of the March meeting of an ICCVAM-sponsored peer review on an *in vitro* method to identify potential endocrine-active substances. In their comments following this presentation, SACATM members indicated that they felt the peer review panel conducted a comprehensive review of an impressive body of work. Summary presentations were also given on a September 2010 NICEATM-ICCVAM workshop on alternative methods for vaccine potency and safety testing, and workshops convened by NICEATM and ICCVAM in January 2011 on Best Practices for Regulatory Safety Testing. Commenters on these presentations noted that both the vaccine workshop and the Best Practices workshops had provided opportunities for productive interaction between industry representatives and regulators, and made suggestions about how future workshops could be made even more effective.

SACATM also considered nominations that had been forwarded to ICCVAM for activities supporting the further development of *in vitro* test methods for detection and quantification of botulinum neurotoxin and for detection of pyrogenic substances. SACATM endorsed further ICCVAM activity on these nominations with high priority.

Representatives from NIEHS and the National Institutes of Health provided SACATM with summaries of ongoing activities contributing to the development of alternative test methods. SACATM also received updates from representatives of international validation organizations, including the Korean Center for the Validation of Alternative Methods, Health Canada, the Japanese Center for the Validation of Alternative Methods, and the European Centre for the Validation of Alternative Methods.

Materials from the June SACATM meeting, including the agenda, background materials, public comments submitted, and all presentations, are available on the NTP website at <http://ntp.niehs.nih.gov/go/8202>. Minutes from the meeting will be available on this page later this fall.

### **NICEATM and ICCVAM convene Workshop on Rabies Vaccine Testing**

NICEATM and ICCVAM convened an "International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward" on October 11-13, 2011, at the U.S. Department of Agriculture Center for Veterinary Biologics in Ames, Iowa. This workshop brought together international scientific experts from government, industry, and academia to review the available methods and approaches that reduce, refine (decrease or eliminate pain and distress), and replace animals used in human and veterinary rabies vaccine potency testing. Participants then developed an implementation strategy to achieve global acceptance and use of these alternatives.

Along with NICEATM and ICCVAM, the workshop was co-sponsored by the European Centre for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, and Health Canada. The workshop featured 17 speakers from nine countries and three breakout sessions that allowed participants to discuss the key issues to be addressed at the workshop. A poster session planned for the workshop featured presentations on current work on alternative methods that may reduce, refine, or replace the use of animals in rabies vaccine potency testing.

Rabies vaccines serve a vital role in preventing deaths from this fatal disease and controlling rabies in certain animal populations. However, determining the safety and effectiveness of rabies vaccines requires large numbers of laboratory animals and involves significant pain and distress. New methods and approaches are sought that: 1) are more humane and use fewer or no animals, 2) are faster, cheaper, and more accurate, and 3) are safer for laboratory workers. Recent scientific and technological advances may allow several alternative approaches for rabies vaccine potency testing to be implemented immediately or in the near future.



More information about the workshop is available on the NICEATM-ICCVAM website at <http://iccvam.niehs.nih.gov/meetings/RabiesVaccWksp-2011/RabiesVaccWksp.htm>. Presentations from the workshop and a summary of the workshop conclusions will be posted on this page. Proceedings from the workshop will be published next year in the journal *Biologicals*.

### **NICEATM presentations at Eighth World Congress available on website**

Abstracts and posters presented by NICEATM staff at the Eighth World Congress on Alternatives and Animal Use in the Life Sciences are now available on the NICEATM-ICCVAM website.

At the World Congress, NICEATM staff delivered platform presentations on validation of 21<sup>st</sup> century predictive toxicology methods and validation of test methods to identify potential endocrine-active substances. NICEATM staff and ICCVAM members also presented posters that highlighted current activities and test method evaluations. Five of these presentations focused on recent ICCVAM recommendations and international regulatory acceptance for new versions and applications of the murine local lymph node assay to identify substances with the potential to cause allergic contact dermatitis. Other presentations summarized ICCVAM recommendations and regulatory acceptance of alternative methods for ocular safety testing as well as conclusions and recommendations from a NICEATM-sponsored 2010 workshop on alternative methods for vaccine potency and safety testing.

A summary of all NICEATM-ICCVAM activities, including abstracts of poster and platform presentations and copies of all posters, can be found on the NICEATM-ICCVAM website at: <http://iccvam.niehs.nih.gov/meetings/8WC/8WCablst.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 for a test method have been completed that adequately characterize its usefulness and limitations for a specific proposed regulatory requirement or application, 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 are also 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](mailto:niceatm@niehs.nih.gov); phone +1 919 541 2384; fax +1 919 541 0947. Copies of documents mentioned in this update can also 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](http://iccvam.niehs.nih.gov/contact/ni_list.htm)