


**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

**National Toxicology Program (NTP); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Federal Agency Responses to Interagency Coordinating Committee on the Validation of Alternative Methods Recommendations on the Murine Local Lymph Node Assay, An Alternative Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals and Products: Notice of Availability**

**AGENCY:** National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).

**ACTION:** Notice of Availability.

**SUMMARY:** U.S. Federal agency responses to Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) test method recommendations on the murine local lymph node assay (LLNA), an alternative safety testing method used to assess the potential of chemicals and products to cause allergic contact dermatitis (ACD), are now available. ICCVAM recommended an updated LLNA test method protocol, a reduced

LLNA procedure (rLLNA), and LLNA test method performance standards. In accordance with the ICCVAM Authorization Act, ICCVAM previously forwarded recommendations to Federal agencies and made these recommendations available to the public (74 FR 50212). Agencies have now notified ICCVAM in writing of their findings and ICCVAM is making these responses available to the public. Federal agency responses are available on the NICEATM-ICCVAM Web site at <http://iccvam.niehs.nih.gov/methods/immunotox/rLLNA.htm> and [http://iccvam.niehs.nih.gov/methods/immunotox/llna\\_PerfStds.htm](http://iccvam.niehs.nih.gov/methods/immunotox/llna_PerfStds.htm). The ICCVAM recommendations are provided in ICCVAM Test Method Evaluation Reports, which are available on the NICEATM-ICCVAM Web site at <http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-LD/TMER.htm> and <http://iccvam.niehs.nih.gov/methods/immunotox/PerfStds/llna-ps.htm>.

**FOR FURTHER INFORMATION CONTACT:** Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2-16, Research Triangle Park, NC, 27709, (telephone) 919-541-2384, (fax) 919-541-0947, (e-mail) [niceatm@niehs.nih.gov](mailto:niceatm@niehs.nih.gov). Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

**SUPPLEMENTARY INFORMATION:**

## Background

ICCVAM originally recommended the LLNA as a valid stand-alone alternative method to existing ACD test methods in 1999 (NIH publication No. 99-4494; available at [http://iccvam.niehs.nih.gov/docs/immunotox\\_docs/llna/llnarep.pdf](http://iccvam.niehs.nih.gov/docs/immunotox_docs/llna/llnarep.pdf)). ICCVAM recommended that the LLNA could be used as a substitute for the existing guinea pig based test methods for most testing situations, which would reduce the number of animals required and avoid pain and distress. The Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Consumer Product Safety Commission (CPSC) subsequently accepted the method as a valid substitute. The Organization for Economic Co-operation and Development (OECD) adopted the LLNA as international OECD Test Guideline 429 and the International Standards Organization (ISO) adopted the LLNA as ISO Test 10993-10.

The updated LLNA test method protocol uses 20% fewer animals than the original LLNA protocol recommended by ICCVAM in 1999, and provides improved guidance on dose selection and other procedures to improve assay accuracy and reproducibility. The rLLNA procedure can further reduce the number of animals required by 40% compared to the updated LLNA protocol multi-dose procedure. ICCVAM recommends that the rLLNA test method should be routinely considered before conducting the traditional multi-dose LLNA, and should be used as the initial test for ACD where determined appropriate. ICCVAM evaluation and complete recommendations for the updated LLNA test method protocol and the rLLNA procedure are provided in the *ICCVAM Test Method Evaluation Report: The Reduced Murine Local Lymph Node Assay: An Alternative Test Method Using Fewer Animals to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products* (NIH Publication No. 09-6439, available at <http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-LD/TMER.htm>).

ICCVAM also recommends that the LLNA test method performance standards can be used to efficiently evaluate the validity of modified test methods that are mechanistically and functionally similar to the traditional LLNA. The LLNA test method performance standards are provided in the ICCVAM report, *Recommended Performance Standards: Murine Local Lymph Node Assay* (NIH Publication No. 09-7357, available at <http://>

[iccvam.niehs.nih.gov/methods/immunotox/PerfStds/llna-ps.htm](http://iccvam.niehs.nih.gov/methods/immunotox/PerfStds/llna-ps.htm)).

ICCVAM evaluated the updated versions of the LLNA in response to a 2007 nomination from the CPSC ([http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC\\_LLNA\\_nom.pdf](http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC_LLNA_nom.pdf)). The nomination also requested that ICCVAM evaluate the validation status of (1) new versions of the LLNA test method protocol that do not require the use of radioactive materials; (2) use of the LLNA to test mixtures, aqueous solutions, metals, and other substances; and (3) use of the LLNA to determine ACD potency categories for hazard classification and labeling purposes. ICCVAM recommendations on these new versions and applications are undergoing finalization and will be forwarded to Federal agencies in 2010.

## Agency Responses to ICCVAM Recommendations

In September 2009, ICCVAM forwarded final test method recommendations for the rLLNA, the updated LLNA test method protocol, and LLNA performance standards to U.S. Federal agencies for consideration, in accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C. 285-3(e)(4)) (74 FR 50212). The ICCVAM Authorization Act requires member agencies to review ICCVAM test method recommendations and notify ICCVAM in writing of their findings no later than 180 days after receipt of recommendations. The Act also requires ICCVAM to make ICCVAM recommendations and agency responses available to the public. Agency responses are to include identification of relevant test methods for which the ICCVAM test method recommendations may be added or substituted, and indicate any revisions or planned revisions to existing guidelines, guidances, or regulations to be made in response to these recommendations.

## Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use, generate, or disseminate toxicological information. ICCVAM conducts technical evaluations of new, revised, and alternative methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological test methods that more accurately assess the safety and hazards of chemicals and products and that refine, reduce, and replace animal use. The ICCVAM Authorization Act of 2000 established ICCVAM as a

permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM and provides scientific and operational support for ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of U.S. Federal agencies. Additional information about ICCVAM and NICEATM can be found on their Web site (<http://www.iccvam.niehs.nih.gov>).

Dated: April 30, 2010.

**John R. Bucher,**

*Associate Director, National Toxicology Program.*

[FR Doc. 2010-10954 Filed 5-7-10; 8:45 am]

**BILLING CODE 4140-01-P**