DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); the Murine Local Lymph Node Assay: Request for Comments, Nominations of Scientific Experts, and Submission of Data

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

ACTION: Request for comments, submission of relevant data, and nominations of scientific experts.

SUMMARY: The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) received a nomination from the U.S. Consumer Product Safety Commission (CPSC) to evaluate the validation status of: (1) The murine local lymph node assay (LLNA) as a stand-alone assay for determining potency (including severity) for the purpose of hazard classification; (2) the ''cut-down'' or ''limit dose'' LLNA approach; (3) non-radiolabeled LLNA methods; (4) the use of the LLNA for testing mixtures, aqueous solutions, and metals; and (5) the current applicability domain (i.e., the types of chemicals and substances for which the LLNA has been validated). ICCVAM reviewed the nomination, assigned it a high priority, and proposed that NICEATM and ICCVAM carry out the following activities in its evaluation: (1) Initiate a review of the current literature and available data, including the preparation of a comprehensive background review document, and (2) convene a peer review panel to review the various proposed LLNA uses and procedures for which sufficient data and information are available to adequately assess their validation status. ICCVAM also recommends development of performance standards for the LLNA. At this time, NICEATM requests: (1) Public comments on the appropriateness and relative priority of these activities, (2) nominations of expert scientists to consider as members of a possible peer review panel, and (3) submission of data for the LLNA and/or modified versions of the LLNA.

DATES: Submit comments, data, and nominations by June 15, 2007. Relevant data will also be accepted after this date and considered when feasible.

ADDRESSES: Dr. William S. Stokes, NICEATM Director, NIEHS, P.O. Box 12233, MD EC–17, Research Triangle Park, NC 27709, (fax) 919–541–0947, (e-mail) *niceatm@niehs.nih.gov.* Courier address: NICEATM, 79 T.W. Alexander Drive, Building 4401, Room 3128, Research Triangle Park, NC 27709. Responses can be submitted electronically at the ICCVAM–NICEATM Web site: *http://iccvam.niehs.nih.gov/contact/FR_pubcomment.htm* or by e-mail, mail, or fax.

FOR FURTHER INFORMATION CONTACT: Other correspondence should be

directed to Dr. William S. Stokes (919–541–2384 or *niceatm@niehs.nih.gov*).

SUPPLEMENTARY INFORMATION:

Background

ICCVAM previously evaluated the validation status of the LLNA as a stand-alone alternative method to the Guinea Pig Maximization Test (GPMT) and the Buehler Assay (NIH publication No. 99–4494; available at *http://iccvam.niehs.nih.gov/methods/immunotox/llna.htm*). Based on this evaluation, ICCVAM recommended the LLNA as a valid substitute for the guinea pig methods for most testing situations. The Environmental Protection Agency, Food and Drug Administration, and the CPSC subsequently accepted the method as a valid substitute. The OECD also adopted the LLNA as OECD Test Guideline 429.

In January 2007, the CPSC submitted a nomination to NICEATM (*http://iccvam.niehs.nih.gov/SuppDocs/submission.htm*) requesting that ICCVAM assess the validation status of:

- The LLNA as a stand-alone test for potency determinations (including severity) for the purpose of hazard classification.
- LLNA protocols that do not require the use of radioactive materials.
- The LLNA ''cut-down'' or ''limit dose'' procedure.
- The ability of the LLNA to test mixtures, aqueous solutions, and metals.
- The current applicability domain (i.e., the types of chemicals and substances for which the LLNA has been determined to be useful).

Since 2003, ICCVAM has routinely developed performance standards for test methods; however, they were not developed for the LLNA, which was reviewed in 1999. Accordingly, ICCVAM proposes to now develop performance standards for the LLNA. Performance standards communicate the basis by which new proprietary and nonproprietary test methods have been determined to have sufficient relevance and reliability for specific testing purposes. Performance standards based on test methods accepted by regulatory agencies can be used to evaluate the reliability and relevance of other test methods that are based on similar scientific principles and measure or predict the same biological or toxic effect. On January 24, 2007, ICCVAM unanimously endorsed with a high priority: (1) Developing performance standards for the LLNA and (2) initiating a review of the available data and information associated with the CPSC nominated activities. A determination of which (if any) of the nominated activities will move forward will be made subsequent to this review and after consideration of comments by the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). If a decision is made to proceed with evaluation of these test methods, ICCVAM and NICEATM propose convening a peer review panel to review the usefulness and limitations of each of the LLNA methods listed above. The panel would also formulate conclusions on the adequacy of draft ICCVAM performance standards, any proposed future validation studies, and draft ICCVAM-proposed standardized test method protocols.

Request for Public Comments and Nominations of Scientific Experts

NICEATM requests public comments on the appropriateness and relative priority of the nominated activities. NICEATM also requests the nominations of scientists with relevant knowledge and experience to serve on the panel if a panel meeting occurs. Areas of relevant expertise include, but are not limited to: physiology, pharmacology, immunology, skin sensitization testing in animals, development and use of in vitro methodologies, biostatistics, knowledge about the use of chemical datasets for validation of toxicity studies, and hazard classification of chemicals and products. Each nomination should include the person's name, affiliation, contact information (i.e., mailing address, e-mail address, telephone and fax numbers), curriculum vitae, and a brief summary of relevant experience and qualifications.

Request for Data

NICEATM invites the submission of data from standard LLNA testing (i.e., OECD TG 429) with mixtures, aqueous solutions, and/or metals, as well as corresponding data from human and other animal studies. In addition, NICEATM invites the submission of data supporting the use of (1) the LLNA as a stand-alone test for determining potency (including severity) for the purpose of hazard classification, (2) the LLNA ''cut-down'' or ''limit dose'' procedure, and (3) LLNA protocols that do not require the use of radioactivity. Although data can be accepted at any time, data submitted by June 15, 2007, will be considered during the ICCVAM evaluation process. Submitted data will be used to further evaluate the usefulness and limitations of the LLNA and may be incorporated into future NICEATM and ICCVAM reports and publications as appropriate. The data will also be included in a database to support the investigation of other test methods for assessing skin sensitization.

When submitting chemical and protocol information/test data, please reference this **Federal Register** notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, as applicable).

NICEATM prefers data to be submitted as copies of pages from study notebooks and/or study reports, if available. Raw data and analyses available in electronic format may also be submitted. Each submission for a chemical should preferably include the following information, as appropriate:

- Common and trade name.
- Chemical Abstracts Service Registry Number (CASRN).
- Chemical class.
- Product class.
- Commercial source.
- LLNA protocol used.
- Individual animal responses.
- The extent to which the study complied with national or international Good Laboratory Practice (GLP) guidelines.
- Date and testing organization.
- Sensitization data from other test methods.

Consideration by SACATM

On June 12, 2007, SACATM will meet at the Marriott Bethesda North Hotel and Conference Center in Bethesda, Maryland. The agenda includes consideration of the nominated LLNA activities, priorities, and proposed activities *http://ntp.niehs.nih.gov/go/7441*) and an opportunity for oral public comments. The SACATM meeting was announced in a separate **Federal Register** notice (**Federal Register** Vol. 72, No. 83, pp. 23831–32, May 1, 2007).

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 federal regulatory and research agencies that use or generate 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, or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes 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 federal agencies. Additional information about ICCVAM and NICEATM is available on the following Web site: *http://iccvam.niehs.nih.gov*.

Dated: May 8, 2007.

David A. Schwartz,

Director, National Institute of Environmental Health Sciences and National Toxicology Program.

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