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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Recommendations on the Use of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis: Availability of Federal Agency Responses

AGENCY: Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH)

ACTION: Availability of Agency Responses

SUMMARY: The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces availability of U.S. Federal agency responses to ICCVAM test method recommendations on the use of the murine local lymph node assay (LLNA) for potency categorization of chemicals causing allergic contact dermatitis (ACD). ICCVAM forwarded the recommendations to Federal agencies and made these recommendations available to the public (76 FR 45254). In accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*–3), agencies have 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 website at *http://iccvam.niehs.nih.gov/methods/immunotox/LLNApotency.htm*. The ICCVAM recommendations are provided in the ICCVAM test method evaluation report (ICCVAM, 2011). **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, (email) *niceatm@niehs.nih.gov*. Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

SUPPLEMENTARY INFORMATION:

Background

The LLNA is accepted worldwide as a valid alternative to traditionally accepted guinea pig test methods for assessing ACD hazard potential for most testing applications. In January 2007, the U.S. Consumer Product Safety Commission (CPSC) requested that NICEATM and ICCVAM evaluate the LLNA for its usefulness for determining skin sensitization potency categories. The CPSC, under the Federal Hazardous Substances Act, requires hazard labeling of products considered to be strong skin sensitizers. Results from tests that could be used to identify potential strong human skin sensitizers would support the CPSC and other agencies with an interest in identifying strong skin sensitizers. While guinea pig tests have traditionally been used to categorize the potency of skin sensitizers, the LLNA uses fewer animals, requires less time to perform, provides dose-response information, and eliminates the pain and distress produced by positive reactions.

Accordingly, NICEATM and ICCVAM evaluated the extent that the LLNA could be used to correctly predict "strong" versus "other than strong" human skin sensitizers. NICEATM, working in collaboration with the ICCVAM Interagency Immunotoxicity Working Group (IWG), prepared a draft background review document (BRD) and draft recommendations for use of the LLNA for potency categorization of chemicals that cause ACD in humans. The draft BRD and draft ICCVAM recommendations were reviewed in a public meeting of an international independent scientific peer review panel in March 2008; the peer review panel

report was made available to the public for comment in May 2008 (73 FR 29136). The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) discussed and commented on the report, draft BRD, and draft ICCVAM recommendations at its June 2008 meeting (73 FR 25754). ICCVAM considered the panel's report, comments from SACATM, and public comments, and finalized its recommendations.

The final ICCVAM recommendations are provided in the *ICCVAM Test Method Evaluation Report: Usefulness and Limitations of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in Humans* (NIH Publication No. 11-7709, available at *http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-pot/TMER.htm*). The test method evaluation report also includes an updated ICCVAM-recommended LLNA protocol and recommended future studies that may further characterize the usefulness and limitations of the LLNA for potency determinations. The final BRD, including additional analyses performed by NICEATM as recommended by the peer review panel, is included as an appendix to the test method evaluation report. ICCVAM recommended that positive results from ACD safety testing using the murine LLNA could be used to categorize some chemicals and products as strong skin sensitizers. However, since the current LLNA decision criterion only identified 52% of the strong human skin sensitizers, ICCVAM recommended that this criterion should not be used as the basis for determining that a substance is not a strong skin sensitizer. Therefore, the potency criterion should only be used in a screening approach, where chemicals that meet the criterion could be categorized as strong skin sensitizers, but chemicals that do not meet the criterion would require additional testing or information to determine that they are not strong skin sensitizers. In accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and Animal Welfare Act regulations, 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 unrelieved pain and distress, and should be used when determined appropriate.

Agency Responses to ICCVAM Recommendations

In June 2011, ICCVAM forwarded final test method recommendations on using the LLNA for potency categorization of chemicals to U.S. Federal agencies for consideration (76 FR 45254), in accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*–3). 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. Complete agency responses are available at *http://iccvam.niehs.nih.gov/methods/immunotox/LLNApotency.htm*.

Background Information on NICEATM, ICCVAM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological and safety testing methods that more accurately assess the safety and hazards of chemicals and products while reducing animal use, refining animal use by enhancing animal welfare and lessening or avoiding unrelieved pain and

distress, or replacing animals used for testing. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*–3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods and strategies applicable to the needs of U.S. Federal agencies. NICEATM and ICCVAM welcome the public nomination of new, revised, and alternative test methods and strategies for validation studies and technical evaluations. Additional information about ICCVAM and NICEATM can be found on the NICEATM–ICCVAM website (*http://iccvam.niehs.nih.gov*).

SACATM was established in response to the ICCVAM Authorization Act [Section 285*l*-3(d)] and is composed of scientists from the public and private sectors (67 FR 11358). SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at *http://ntp.niehs.nih.gov/go/167*.

Reference

ICCVAM. 2011. ICCVAM Test Method Evaluation Report: Usefulness and Limitations of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in Humans. NIH Publication No. 11-7709. Research

Triangle Park, NC: National Institute of Environmental Health Sciences. Available: *http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-pot/TMER.htm.*

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