DEPARTMENT OF HEALTH AND HUMAN SERVICES

Report and Recommendations on the Usefulness and Limitations of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in Humans

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

ACTION: Availability of Report and Recommendations; Notice of Transmittal.

SUMMARY: The NTP Interagency Center for the Evaluation of Alternative Test Methods (NICEATM) announces availability of an Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) test method evaluation report (TMER) that includes recommendations on the usefulness and limitations of the local lymph node assay (LLNA) for categorizing the potency of substances with the potential to cause allergic contact dermatitis (ACD) as strong skin sensitizers. Strong skin sensitizers are substances considered to have a significant potential for causing ACD.

ICCVAM recommends that a specific potency criterion for positive results from ACD safety testing using the LLNA can be used to further categorize some chemicals and products as strong skin sensitizers. However, since this criterion only identified approximately half of strong human skin sensitizers, ICCVAM concluded that failure to meet this criterion cannot 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.

The report and recommendations have been transmitted to Federal agencies for their review and response to ICCVAM in accordance with the provisions of the ICCVAM

Authorization Act of 2000 (42 U.S.C. 285l-2).

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. Courier address:* NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

SUPPLEMENTARY INFORMATION:

Background

In 1999, ICCVAM evaluated the validation status of the LLNA as a stand-alone alternative test method to the guinea pig maximization test (GPMT) and the Buehler test (BT) for assessing the ACD hazard potential of products and chemicals (NIH Publication No. 99–4494; *http://iccvam.niehs.nih.gov/methods/immunotox/llna_PeerPanel98.htm*). Based on this evaluation, ICCVAM recommended the LLNA as a valid substitute for traditional guinea pig test methods for most testing situations. The U.S. Environmental Protection Agency, the U.S. Food and Drug Administration, and the U.S. Consumer Product Safety Commission (CPSC) subsequently accepted the method as a valid substitute for the GPMT and BT. The Organisation for Economic Co-operation and Development (OECD) also adopted the LLNA as OECD Test Guideline 429 in 2002. Using the LLNA instead of guinea pig tests reduces and refines (decreases or eliminates pain and distress) animal use for ACD safety testing.

In 2007, the CPSC nominated several new versions and applications of the LLNA to ICCVAM for evaluation of their scientific validity for regulatory testing purposes (*http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC_LLNA_nom.pdf*). The nomination requested that ICCVAM assess (1) the validation status of the LLNA limit dose procedure (*i.e.,* the reduced LLNA); (2) the modified LLNA test method protocols that do not require the use of radioactive materials; (3) the use of the LLNA to test mixtures, aqueous solutions, and metals; and (4) the use of the LLNA as a stand-alone assay to determine ACD potency categories for hazard classification and labeling. NICEATM published a **Federal Register** notice (72 FR 27815) requesting public comments on (1) The appropriateness and relative priority of the CPSC-nominated LLNA activities, (2) the nomination of scientists to serve on an international independent scientific peer review panel, and (3) the submission of data from LLNA testing that related to the CPSC-nominated LLNA activities as well as corresponding data from human and other animal studies. ICCVAM assigned these activities a high priority after considering comments from the public and endorsement from the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). NICEATM and ICCVAM compiled comprehensive draft background review documents (BRDs), released them for public comment in January 2008 (73 FR 1360), and convened a public meeting of the panel on March 4–6, 2008, to peer review the draft documents. The panel evaluated the information in the draft BRDs as to whether it supported draft ICCVAM recommendations for (1) Test method usefulness and limitations, (2) updated standardized test method protocols, and (3) proposed future studies. The panel considered public comments made at the meeting, as well as public comments submitted in advance of the meeting, before concluding their deliberations. The panel's report was made available in May 2008 (73 FR 29136) for public comment. The draft ICCVAM BRDs, draft ICCVAM test method recommendations, the panel's report, and all public comments were made available to SACATM for comment at its meeting on June 18–19, 2008 (73 FR 25754).

After considering the conclusions and recommendations of the panel, comments from SACATM, and public comments, ICCVAM forwarded final recommendations for the reduced LLNA (NIH Publication No. 09–6439; *http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-LD/TMER.htm*), LLNA performance standards, and the updated LLNA test method protocol (NIH Publication No. 09–7357; *http://iccvam.niehs.nih.gov/methods/immunotox/llna_PerfStds.htm*) to Federal agencies in September 2009 (74 FR 50212). Agency responses are available on the NICEATM–ICCVAM Web site.

NICEATM subsequently obtained additional data and/or information and revised the draft BRDs for both the traditional and nonradioactive LLNA methods. ICCVAM released the revised draft BRDs and the revised draft ICCVAM test method recommendations to the public for comment and announced a second meeting of the panel (74 FR 8974). The panel reconvened in public session on April 28–29, 2009, to review the ICCVAM-revised draft documents and to finalize its conclusions and recommendations on the current validation status of the nonradioactive test methods and the expanded uses of the LLNA for pesticide formulations and other products. The panel's report was made available for public comment in June 2009 (74 FR 26242). The revised draft ICCVAM BRDs, revised draft ICCVAM test method recommendations, the panel's report, and all public comments were made available to SACATM for comment on June 25–26, 2009 (74 FR 19562).

After considering the conclusions and recommendations of the panel, comments from SACATM, and public comments, along with the recommendations of an OECD Expert Consultation on the LLNA convened in October and December 2009, ICCVAM finalized and forwarded test method recommendations on two nonradioactive versions of the LLNA, LLNA: 5-Bromo-2′-deoxyuridine-Enzyme-Linked Immunosorbent Assay (BrdU–ELISA) (NIH Publication No. 10–7552; *http://iccvam.niehs.nih.gov/methods/immunotox/llna-ELISA/TMER.htm*) and LLNA: Daicel Adenosine Triphosphate (DA) (NIH Publication No. 10–7551; *http://iccvam.niehs.nih.gov/methods/immunotox/llna-DA/TMER.htm*), and expanded uses of the LLNA for pesticide formulations and other products (NIH Publication No. 10–7512; *http://iccvam.niehs.nih.gov/methods/immunotox/llna-app.htm*) to Federal agencies in June 2010 (75 FR 37443). Agency responses to these ICCVAM test method recommendations are available on the NICEATM–ICCVAM Web site.

The ICCVAM TMER, *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), describes ICCVAM's recommendations for using LLNA test results to categorize the potency of some substances identified as having the potential to cause ACD in humans as strong skin sensitizers. Strong sensitizers are those substances considered to have a significant potential for causing hypersensitivity. ICCVAM recommends that a specific potency criterion for positive results from ACD safety testing using the LLNA can be used to further categorize some chemicals and products as strong skin sensitizers. However, since this criterion only identified approximately half of the strong human skin sensitizers tested, failure to meet this criterion cannot 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.

The ICCVAM evaluation found that only 52% of the strong human skin sensitizers in the validation database would be identified as strong skin sensitizers using the LLNA potency criterion in the 2009 United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Accordingly, chemicals that do not meet the criterion would require additional testing or information to determine that a substance is not a strong human skin sensitizer.

Background Information on ICCVAM, NICEATM, 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 and that reduce, refine (decrease or eliminate pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–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 welcome the public nomination of new, revised, and alternative test methods and strategies applicable to the needs of U.S. Federal agencies. Additional information about NICEATM and ICCVAM can be found on the NICEATM–ICCVAM Web site (*http://iccvam.niehs.nih.gov*).

SACATM was established in response to the ICCVAM Authorization Act [Section 285l–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.*

References

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