DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
NTP Interagency Center for the Evaluation
of Alternative Toxicological Methods
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MEMORANDUM

DATE: August 5, 2011

TO: The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

FROM: Director, National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP)

SUBJECT: NIEHS Response to ICCVAM Test Recommendations Relevant to Allergic Contact Dermatitis (ACD) Hazard Testing and Identification of Strong Sensitizers

On June 30, 2011, at the request of the Secretary of the Department of Health and Human Services, I forwarded toxicological test recommendations from ICCVAM to 14 Federal agencies for their consideration. The recommendations were developed and transmitted pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test recommendations and notify ICCVAM in writing of their findings, including identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted. This memorandum provides the NIEHS response to ICCVAM regarding the test recommendations.

ICCVAM provided recommendations for using murine local lymph node assay (LLNA) test results to categorize some substances as strong skin sensitizers. Strong sensitizers are those substances considered to have a significant potential for causing skin hypersensitivity resulting in ACD in humans. Recommendations were provided in the report, *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).

NIEHS agrees with the ICCVAM test recommendation that the LLNA can be used to categorize some chemicals and products as strong skin sensitizers using a criterion published in the 2009 United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS). 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. NIEHS concludes that the available data support the ICCVAM recommendation that the GHS 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.

NIEHS is concerned by the ICCVAM finding that only 52% of the strong human skin sensitizers in the validation database would be identified as strong skin sensitizers using the GHS criterion for the LLNA. Accordingly, NIEHS agrees with ICCVAM that the GHS potency criterion should reflect that 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. Consideration should be given to updating the next version of the GHS to reference and reflect the findings and recommendations provided in the ICCVAM report. NIEHS recommends that ICCVAM should serve as an interagency forum for further technical evaluation of these issues and that ICCVAM, together with the NTP Interagency Center for the Evaluation of Alterative Methods (NICEATM), should provide technical and scientific support necessary to resolve the issue in a manner that will ensure that the current level of protection for consumers and workers is not reduced.

NIEHS is not a regulatory agency and therefore does not promulgate regulatory testing requirements or guidelines for which the ICCVAM recommendations may be applicable. However, NIEHS does conduct ACD testing as part of its NTP activities. Therefore, NIEHS and the NTP will ensure that the LLNA test method protocol is routinely considered whenever studies are proposed to assess ACD and to categorize the potency of substances identified as having the potential to cause ACD in humans.

NIEHS and NTP scientists and the NIEHS Institutional Animal Care and Use Committee (IACUC) have been informed about the availability, usefulness, and limitations of the LLNA for potency categorization of chemicals causing ACD in humans. They have also been advised that the LLNA should be routinely considered when planning animal studies to evaluate the ACD hazard potential and potency of chemicals and products in order to minimize animal use and to avoid pain and distress. To comply with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and applicable USDA Animal Welfare Act Regulations, the NIEHS IACUC has also been asked to ensure that the LLNA is always considered whenever applicable, and to ensure that it is used when determined appropriate.

NIEHS appreciates ICCVAM's comprehensive evaluation of the LLNA and other ongoing NICEATM and ICCVAM activities to advance alternative methods. NIEHS remains highly committed to the development, validation, and regulatory acceptance of scientifically sound alternative safety testing methods that will support improved protection of people, animals, and the environment while providing for improved animal welfare.

/s/

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.

cc:
Dr. John Bucher, Director, Divison of the NTP
Dr. William Stokes, Executive Director, ICCVAM
Dr. Jodie Kulpa-Eddy, Chair, ICCVAM