DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
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MEMORANDUM

DATE: December 7, 2010

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

FROM: Director, National Institute of Environmental Health Sciences and the National Toxicology Program

SUBJECT: NIEHS Response to ICCVAM Test Recommendations on Nonradioactive Versions and New Applications of the Murine Local Lymph Node Assay

On June 10, 2010, at the request of the Secretary of the Department of Health and Human Services, I forwarded toxicological test recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICVAM) 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. 285*l*-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 two nonradioactive versions of the murine local lymph node assay (LLNA) that can be used to reduce and refine (less pain and distress) animal use for testing necessary to assess whether chemicals and products have the potential to cause allergic contact dermatitis (ACD). ICCVAM also provided recommendations for broader applications of the LLNA for other types of chemicals and products.

NIEHS agrees with the ICCVAM test recommendations for the two nonradioactive versions of the LLNA: the LLNA: BrdU-ELISA and the LLNA: DA. Since these methods do not require the use of radioactive reagents, they provide advantages in terms of reduced hazardous waste compared to the traditional LLNA. Furthermore, the availability of these non-radioactive versions will allow for broader use of the LLNA because they can now be used by laboratories that could not previously use the LLNA because they were not able to use radioactive reagents.

NIEHS agrees with the ICCVAM recommendations that the accuracy and reliability of the LLNA: BrdU-ELISA and LLNA: DA support their use to evaluate the potential for chemicals and products to cause allergic contact dermatitis in most testing situations. These methods should therefore always be considered whenever allergic contact dermatitis testing is proposed, and they should be used when determined appropriate. The ICCVAM-recommended LLNA: BrdU-ELISA and LLNA: DA test method protocols incorporate all relevant aspects of the recently updated ICCVAM-recommended traditional LLNA test method protocol (NIH

Publication 09-7357), and should therefore be used for such testing. The respective protocols also include reduced LLNA: BrdU-ELISA and LLNA: DA procedures that should also always be considered and used where determined appropriate because the procedures reduce animal use by an additional 40% compared to the standard test protocol.

NIEHS agrees with the ICCVAM recommendations for expanded applications of the LLNA. NIEHS concludes that available data support the use of the LLNA for assessing the allergic contact dermatitis potential of pesticide formulations, metals with the exception of nickel, substances tested in aqueous solutions, and other products and substances unless there are unique physicochemical properties associated with these materials that may interfere with the ability to obtain accurate results in the LLNA. NIEHS also agrees that to achieve adequate dermal exposure of aqueous solutions, these must be tested in an appropriate vehicle that will maintain sufficient contact of the test article with the skin.

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 allergic conduct dermatitis testing as part of its National Toxicology Program (NTP) activities. Therefore, NIEHS and the NTP will ensure that the non-radioactive LLNA test method protocols are routinely considered whenever studies are proposed to assess allergic contact dermatitis, and will ensure that they are used when determined scientifically appropriate.

NIEHS and the NTP will promote and encourage use of the standard and nonradioactive versions of the LLNA for assessing the allergic contact dermatitis potential of chemicals and products. Accordingly, NIEHS and NTP scientists and the NIEHS Institutional Animal Care and Use Committee (IACUC) have been informed about the availability of these test methods and the expanded LLNA applicability domain. They have also been advised that these alternative methods should be routinely considered when planning animal studies to evaluate the allergic contact dermatitis hazard potential 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 these alternative methods are always considered whenever applicable and to ensure that the methods are used when determined appropriate.

NIEHS appreciates ICCVAM's comprehensive evaluation of these alternative safety testing methods and other ongoing 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/

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cc:
Dr. John Bucher, Associate Director, NTP
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