DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709
http://www.niehs.nih.gov

September 18, 2009

The Honorable Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
HF-1, Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Hamburg:

I am pleased to forward toxicological test method recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for your consideration. These test method recommendations are being sent to you for action pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3).

The test method recommendations are for the reduced murine local lymph node assay (rLLNA), an updated LLNA test method protocol, and LLNA test method performance standards. The LLNA is a test method used to assess the potential for chemicals and products to cause allergic contact dermatitis (ACD). Detailed recommendations for the rLLNA and the updated test method protocol are provided in the report, *ICCVAM Test Method Evaluation Report: The Reduced Murine Local Lymph Node Assay: An Alternative Test Method Using Fewer Animals to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products* (NIH Publication No. 09-6439, Enclosure 1). The LLNA test method performance standards are provided in the report, *Recommended Performance Standards: Murine Local Lymph Node Assay* (NIH Publication No. 09-7357, Enclosure 2).

ICCVAM evaluated these test methods in response to their nomination by the U.S. Consumer Product Safety Commission. The evaluation process included scientific peer review by an independent panel and opportunity for comments from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a federally chartered advisory group for ICCVAM. ICCVAM considered the peer review panel report, all public comments, and the comments of SACATM in preparing the ICCVAM final test method recommendations.

ICCVAM concluded that the scientific validity of the rLLNA has been adequately evaluated and that the performance of the rLLNA, when conducted in accordance with the updated ICCVAM-recommended LLNA test method protocol, is sufficient to distinguish between skin sensitizers and non-sensitizers for testing situations that do not require dose-response information. ICCVAM also concluded that the rLLNA reduces animal use by 40% for each test compared to the traditional multiple-dose LLNA. In order to minimize animal use, ICCVAM recommends that the rLLNA test method should be routinely used as the initial test to determine the ACD potential of chemicals and products for which dose-response information is required, except when such substances are suspected of having the potential to produce ACD. The updated LLNA test method protocol provides for a 20% reduction in the number of animals required compared to the previously recommended traditional LLNA protocol. The rLLNA evaluation report provides the updated LLNA test method protocol which

includes the procedures for conducting the rLLNA, the final ICCVAM rLLNA Background Review Document, relevant skin sensitization regulations and testing guidelines, applicable *Federal Register* notices, public comments, and SACATM meeting minutes.

ICCVAM is also recommending LLNA test method performance standards that can be used to more efficiently evaluate the validity of modified test methods that are similar to the traditional LLNA. The LLNA test method performance standards are based on the performance of the traditional LLNA and the procedures provided in the ICCVAM-recommended updated LLNA test method protocol.

Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test method recommendations and notify ICCVAM in writing of their findings, including identification of relevant test methods for which the ICCVAM test method recommendations may be added or substituted, no later than 180 days after receipt of the recommendations. Agencies are requested to indicate any revisions or planned revisions to existing guidelines, guidances, or regulations made in response to these recommendations.

Please send your agency's response to Rear Admiral William S. Stokes, Director, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS, P.O. Box 12233, Mail Code K2-16, Research Triangle Park, NC 27709, telephone: 919-541-2384, facsimile: 919-541-0947, email: *stokes@niehs.nih.gov*. ICCVAM is required to make the final ICCVAM test method recommendations and the responses from agencies regarding such recommendations available to the public per Section 3(e)(6) of the Act. Accordingly, your response will be made available on the NICEATM-ICCVAM website at *http://iccvam.niehs.nih.gov*.

I appreciate your agency's participation on ICCVAM. The committee serves an important role in facilitating the scientific evaluation and adoption of test methods that will help protect human health and the environment while providing for improved animal welfare whenever possible.

Sincerely,

/s/

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

Enclosures

cc:
Suzanne Fitzpatrick, Ph.D., D.A.B.T., FDA ICCVAM Principal Agency Representative