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

June 30, 2011

The Honorable Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue, Room 2217
Silver Spring, Maryland 20993

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) and 4(a)-(e) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3).

The recommendations are for a specific criterion for the murine local lymph node assay (LLNA) to be used in potency categorization of chemicals that may cause allergic contact dermatitis (ACD) in humans. Detailed recommendations are provided in the enclosed report. The ICCVAM evaluation process included scientific peer review by an international independent panel, review by the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), and multiple public commenting opportunities. ICCVAM considered the peer review report, SACATM comments, and public comments in preparing the final ICCVAM test method recommendations.

In the report, 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.

An important issue revealed by the evaluation is that only 52% of the strong human skin sensitizers in the validation database would be identified as strong skin sensitizers by the LLNA potency criterion in the 2009 United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS). It is important that this finding be considered, along with the recommendation that additional testing or information be required to determine that a substance is not a strong human skin sensitizer. The GHS is currently under consideration for adoption by Federal agencies. 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.

Pursuant to Sections 4(a)-(e), of the ICCVAM Authorization Act, Federal agencies are required to review ICCVAM test method recommendations and notify ICCVAM in writing of the agency's findings no later than 180 days after receipt of this letter. In accordance with these requirements, please include the following information in your response:

1) **Identification of Tests.** Identify the relevant test methods specified in a regulation or industry-wide guideline that specifically or in practice, requires, recommends, or encourages the use of an animal toxicological test method for which the current ICCVAM test recommendations may be added or substituted.

2) **Alternatives**. Describe how your agency will promote and encourage the use of these alternative test methods for the purpose of complying with Federal statutes, regulations, guidelines, or recommendations.

3) **Recommendations Adoption**. State whether your agency will adopt the ICCVAM test method recommendation or whether your agency determines that one or more of the criteria in Section 4(e)(1) to (4) for not adopting the recommendations are met.

Please send your agency's response regarding each of the requirements to RADM William S. Stokes, Director, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (contact information, NICEATM, NIEHS, P.O. Box 12233, 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,

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

Enclosure

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