



National Institutes of Health
National Institute of
Environmental Health Sciences
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June 10, 2010

The Honorable Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Room 2217
Silver Spring, MD 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) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3).

The test method recommendations are for the LLNA: BrdU-ELISA and the LLNA: DA, two nonradioactive versions of the murine local lymph node assay (LLNA), and an expanded LLNA applicability domain. These new versions and applications of the LLNA can be used to further reduce and refine the use of animals for assessing the potential for chemicals and products to cause allergic contact dermatitis (ACD). Detailed recommendations are provided in the enclosed reports.

The evaluation process included scientific peer review by an international 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 concludes that the accuracy and reliability of the LLNA: BrdU-ELISA and LLNA: DA support their use to identify if substances have the potential to cause allergic contact dermatitis. The protocols also include reduced LLNA: BrdU-ELISA and LLNA: DA procedures that should always be considered and used where determined appropriate because they can further reduce animal use by 40% compared to the multi-dose procedure. ICCVAM concludes that available data support the use of the LLNA for testing pesticide formulations, metals with the exception of nickel, substances tested in aqueous solutions, and other substances and products, unless there are unique physicochemical properties associated with these materials that may interfere with the accuracy of the LLNA for identifying substances that have the potential to cause allergic contact dermatitis. ICCVAM also concludes that aqueous solutions must be tested in an appropriate vehicle that will maintain sufficient contact of the test article with the skin.

Pursuant to Sections 4(a-e), of the ICCVAM Authorization Act, agencies are required to:

- 1) No later than 180 days after receipt of ICCVAM test recommendations, identify and forward to the ICCVAM any relevant test method specified in a regulation or industry-wide guideline which specifically, or in practice requires, recommends, or encourages the use of an animal toxicological test method for which the ICCVAM test recommendation may be added or substituted;
- 2) Promote and encourage the use of alternative test methods for the purpose of complying with Federal statutes, regulations, guidelines, or recommendations, if such alternative test methods are found to be effective for generating data in an amount and of a scientific value at least equivalent to the data generated from existing tests for hazard identification, dose-response assessment, or risk assessment purposes;
- 3) Ensure that any new or revised acute or chronic toxicity test method is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method;
- 4) Not later than 180 days after receiving an ICCVAM test recommendation, review such recommendation and notify ICCVAM in writing of its findings; and
- 5) Adopt the ICCVAM test recommendation unless the agency determines that one or more of the criteria in Section 4(e)(1) to (4) are met.

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.
Director, NIEHS and NTP

Enclosures

cc:

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