UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

RADM William S. Stokes, Director
National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods
National Institute of Environmental Health Sciences
P.O. Box 12233, Mail Code K2-16
Research Triangle Park, North Carolina 27709

Dear Dr. Stokes:

This letter is in response to June 30, 2011, request of Dr. Linda S. Birnbaum of the National Institute of Environmental Health Sciences to the Environmental Protection Agency Administrator that EPA review the suitability of the murine lymph node assay to be used in potency categorization of chemicals that may cause allergic contact dermatitis in humans. Staff in EPA's Office of Pesticide Programs found ICCVAM's evaluation and recommendations about the use of the LLNA assay to be technically sound.

However, with respect to the discussion of the use of the LLNA test in the context of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), it is beyond the purview of ICCVAM to develop recommendations for changes in an international agreement or in its interpretation. This issue is properly within the scope of the interagency GHS coordinating group and the individual agencies as they consider adapting the GHS into their regulatory schemes. In addition, based on our internal consultation with GHS experts, it appears that the draft recommendations reflect a fundamental misunderstanding of the GHS classification scheme, which relies on a weight of evidence determination, taking all available evidence into account, and not upon the results of any single test. The GHS hazard communication/label elements are also the same for all sensitizers.

Nonetheless, we will use the technical recommendations from this report and other scientific findings to improve our testing guidelines, inform our discussions with the regulated community and general public and to promote public health protection and the refinement, reduction and ultimate replacement of animals for testing.

In accordance with Sections 4 (a)-(e) of the ICCVAM Authorization Act, we have addressed each of the requirements as follows:

1) **Identification of Tests**: The agency classifies pesticides as either positive sensitizers or negative sensitizers. Thus, the findings of this report will help us prioritize which pesticide active ingredients and formulations need confirmatory testing under EPA's current Skin Sensitization Test Guideline 870.2600.

2) **Alternatives**: A summary of EPA's commitment to promoting and encouraging the use of alternative test methods to comply with federal statutes can be found at http://www.epa.gov/pesticides/science/testing-assessment.html. It includes links to specific activities under way to achieve that goal.

3) **Recommendations Adoption**: The agency concurs with the technical aspects of the recommendation. However, EPA classifies pesticides as either positive sensitizers or negative sensitizers without regard to whether they are strong or weak sensitizers. Thus, the recommendations do not affect our approach as we are already more health protective than specified in the ICCVAM LLNA ACD recommendations.

EPA appreciates the opportunity to review these materials, and we acknowledge the enormous amount of work that went into the evaluation and peer review. We appreciate the time and energy ICCVAM devotes to advancing the "three R" principles of reduction, refinement and replacement of animal use. We look forward to continuing interactions with ICCVAM as part of the Agency's commitment to applying the three R's, where possible, in agency programs.

Sincerely,

/s/

John K. Fowle III, Ph.D., D.A.B.T.
EPA Principal Agency ICCVAM Representative
Health Effects Division (7509-P)
Office of Pesticide Programs

cc: Linda Birnbaum
John Bucher
Steven Bradbury
Jesse Goodman