National Institute for
    Occupational Safety and Health
Centers for Disease Control
    and Prevention (CDC)
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November 3, 2011

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

Dear Dr. Stokes:

As requested by Dr. Linda Birnbaum, Director of National Institute of Environmental
Health Sciences (NIEHS), in her letter of June 30, 2011, the National Institute for
Occupational Safety and Health (NIOSH) is herein responding to you regarding test
method recommendations for using the murine Local Lymph Node Assay (LLNA) for
potency categorization of chemicals that may cause allergic contact dermatitis (ACD).
These methods were recommended by the Interagency Coordinating Committee on the
Validation of Alternative Methods (ICCVAM) in a Test Method Evaluation Report
(TMER).

NIOSH acknowledges the requirement that each agency review these recommended test
methods and notify the ICCVAM regarding test methods for which these alternative
methods may be substituted. NIOSH agrees that the recommended methods are valid but
only for use in screening chemicals, where chemicals that meet the potency 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 a substance is
not a strong sensitizer. The recommended methods are applicable to some NIOSH uses
of the LLNA, and NIOSH scientists participated in the evaluation of the new
recommendations.

1.) Identification of tests. The relevant test method is the LLNA, which is frequently
    used by NIOSH scientists to identify potential sensitizers among chemicals
    encountered in occupational settings or nominated by the National Toxicology
    Program for testing. This TMER recommends a specific use of positive results
    from the LLNA, to categorize the potency of some chemicals as strong
    sensitizers.

2.) Recommendations Adoption. NIOSH is a research agency and has no regulatory testing requirements; however, NIOSH does perform some testing employing the LLNA. The current TMER concluded that when LLNA results for a substance give an EC3 value <2%, it can be classified as a strong sensitizer. Substances with calculated EC3 values >2% would require additional testing for potency categorization. NIOSH agrees with this finding and will use it in data analysis. However, as noted by ICCVAM, the 2% cutoff criterion correctly identified only 52% of strong sensitizers, and our agency will use caution not to exclude potential strong sensitizers based on this criterion. The ICCVAM TMER also states that the test method protocol can reduce the number of required animals per group from five to four, thus reducing the number of animals used in a given test by 20%. In efforts to reduce the number of animals used for testing, our agency will adopt this recommendation.

3.) Alternatives. NIOSH has informed scientists of these new recommendations and will continue to inform them via its Animal Care and Use Committee and training of laboratorians in use of the LLNA. The agency will continue to encourage use or consideration of alternative methods including these, in any animal-using tests that the agency may conduct. NIOSH scientists are currently pursuing research to identify alternative methods (replacing, refining, or reducing the use of animals) to the LLNA, and one potential alternative to the LLNA has already been submitted to the ICCVAM for consideration. NIOSH will attempt to identify and support research programs which may contribute to future development of other alternative test methods.

NIOSH commends the efforts and accomplishments of ICCVAM in reviewing and evaluating these alternative methods and other methods. We are proud of our participation on ICCVAM during its activity as an interagency committee.

Thank you for the opportunity to respond for NIOSH about this ICCVAM achievement.

Sincerely,

/s/

John Howard, M.D.
Director