UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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NTP Interagency Center for the
Evaluation of Alternative Tox. Methods

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Kenneth Olden, Ph.D., Director
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Olden:

You sent Administrator Carol Browner the report, *The Murine Local Lymph Node Assay. A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals/ Compounds*, and accompanying recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). She transferred the letter to the Office of Prevention, Pesticides and Toxic Substances (OPPTS) for reply. We are pleased to have an opportunity to evaluate these products and note that they are very well written; positions are supported by scientific data; and recommendations are reasonable.

EPA has developed a process to evaluate the regulatory acceptability of products coming from ICCVAM . My group, Office of Science Coordination and Policy in OPPTS, is taking the lead in assembling agency review of products, and a committee has been formed to serve this function. Committee members include staff from the science divisions from both the pesticide and toxic substances programs, along with representatives from the water and research and development offices.

Strengths and Weaknesses of the LLNA

The pesticide and toxic substances programs generally are in agreement with the report and the ICCVAM recommendations. We recognize that there are several advantages of the LLNA in comparison to the guinea pig sensitization tests. Items supporting use of the LLNA include such things as

1. The test employs the mouse, the dominant species for immunological studies; this increases the opportunity for further improvement of the protocol given further research.
2. It refines the dermal sensitization test in that it involves only the induction part of sensitization process; this precludes the development of cutaneous inflammation during the elicitation phase that is the endpoint of the guinea pig tests.
3. It potentially reduces the number of animals per test in comparison to the guinea pig tests.
4. It is cost and time effective.
5. Dose-response data are generated.

There are also concerns with the LLNA that reduce its applicability to all test agents. These factors include the following; some may be resolved by the accumulation of more research and testing information.

1. The test is not applicable to metallic compounds.
2. Some test materials may not be easily applied and retained on the ear of the mouse, e.g., volatiles, runny liquids.
3. Certain agents may not be readily absorbed, e.g., highly water soluble or high molecular weight substances.
4. Weak sensitizers may yield false negative test findings, and strong irritants may generate false positive results. However, it is recognized that in the overall assessment of the LLNA, it provides equivalent prediction of human effects compared with the guinea pig methods.
5. Some laboratories may not have the capability to handle radioactive isotopes.
6. Responses from the testing of mixtures have not been well investigated..

EPA Position on the LLNA

In recognition of the advantages and disadvantages of the LLNA, EPA adopts the following positions:

1. The LLNA is acceptable as a free standing test for contact sensitivity in the pesticide and toxic substances programs.
2. The LLNA is the preferred method of testing of materials where there are no reservations concerning its employment.
3. The guinea pig test for dermal sensitization should be retained for those cases where use of the LLNA may not warranted.
4. ICCVAM should consider coalescing federal regulatory programs that have accepted the LLNA to develop a harmonized test protocol, to devise consistent means of scoring and evaluating test results, and to evaluate the handling of some of the weaknesses of the test. Having these products is imperative for registration activities in the pesticide program and for test rules in the toxics program under the Toxic Substances Control Act (TSCA) §4.

   It should be noted, that the toxic substances program does not need a completed protocol for testing under Enforceable Consent Agreements (TSCA §4), for consent orders under TSCA §5(e), or for new chemical submissions under TSCA §5. In the last case, LLNA studies are already being submitted to EPA. The ICCVAM report will improve the program's ability to assess properly the significance of LLNA test findings for any of these applications.
5. Steps should be taken to develop and approve an OECD test guideline for the LLNA.

Thank you for the opportunity to review the LLNA for regulatory acceptability. We look forward to evaluating future products from ICCVAM.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Office of Science Coordination and Policy