Subject: FR Notice Comments - 72FR52130: LLNA Performance Standards
Date: Monday, October 29, 2007 4:31 PM

Dr William S Stokes
Director, NICEATM
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Re: 72 FR 52130; September 12, 2007; National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Draft Performance Standards for the Murine Local Lymph Node Assay: Request for Comments.

Dear Dr. Stokes:

These comments are submitted on behalf of the Alternatives Research and Development Foundation, the American Anti- Vivisection Society, Humane Society Legislative Fund, The Humane Society of the United States, People for the Ethical Treatment of Animals, and the Physicians Committee for Responsible Medicine. The parties to this submission are national animal protection, health, and scientific advocacy organizations with a combined constituency of more than 10 million Americans who share the common goal of promoting reliable and relevant regulatory testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animals.

In January, 2007, (ICCVAM) received a nomination from the U.S. Consumer Product Safety Commission (CPSC) to evaluate the validation status of: (1) The murine local lymph node assay (LLNA) as a stand-alone assay for determining potency (including severity) for the purpose of hazard classification; (2) the "cut-down"˙ or "limit dose" LLNA approach; (3) non-radiolabeled LLNA methods; (4) the use of the LLNA for testing mixtures, aqueous solutions, and metals; and (5) the current applicability domain (i.e., the types of chemicals and substances for which the LLNA has been validated). The development of these performance standards is an initial response to this nomination, and ICCVAM is requesting comment on these performance standards.

Although we fully support the development of performance standards that expedite the validation of new protocols that are similar to previously validated methods, we reiterate our disappointment that ICCVAM/ NICEATM has chosen to apply its limited resources to the lengthy process of developing performance standards for such a narrow scope of applicability. These performance standards apply only to modifications of the "standard LLNA" that involve incorporation of non-radioactive methods of detecting lymphocyte proliferation.

A major aspect of the ICCVAM Authorization Act of 2000 (Public Law 106-545, 42 U.S.C. 285l-3) is the charge to "reduce, refine, and/or replace the use of

animals in testing where feasible." The performance standards described in this FR notice apply to modifications of the standard LLNA that do not affect the number of animals used in this method. The only conceivable reduction could occur if the availability of accepted non-radioactive methods of detection would allow more laboratories to perform the LLNA, and if they then choose the LLNA over the Guinea Pig Maximization test or the Buehler Test. The issue of how this exercise (development of performance standards with this limited applicability) addresses ICCVAM's mandate of reducing, refining or replacing the use of animals is not currently mentioned in the draft document and needs to be adequately explained.

In addition, the draft performance standards require the use of a minimum of 20 reference compounds. The criteria by which the compounds were chosen and the characteristics of the compounds are described; however, there is no justification for the requirement of such a large number of compounds for this particular method modification. The methods to which these performance standards apply will differ from the "standard LLNA" only in the method of detection of lymphocyte proliferation; therefore the element of concern is sensitivity of the detection method. All other aspects of the methods to be evaluated will be identical to the standard LLNA, including delivery and biological response. It is therefore not necessary to test representatives for every chemical class or every solvent that has been tested in the standard LLNA. The important characteristic of the reference compound is the magnitude of proliferation response that is generated, and the list of reference compounds chosen should be limited to those that represent the range of response seen with the standard LLNA.

Finally, it is the belief of the parties to this submission that the limited resources available to ICCVAM/NICEATM would be better spent on activities that would have greater impact on the reduction, refinement or replacement of animal use, such as evaluating the use of human cell lines or one of the available in vitro skin models as a replacement for the LLNA.

Sincerely,

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