UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 24 2003

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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Dear Dr. Stokes:

The Environmental Protection Agency (EPA) recognizes the importance of identifying scientifically sound *in vitro* test methods that have potential to reduce, refine or replace animal usage in toxicity testing. Adequate validation of such methods is critical if the test will be used to support regulatory decision-making. A primary responsibility of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), with assistance from the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), is to shepherd the processes involved in assessing the validation status of test methods which have been recommended or nominated for consideration by the committee and accepted for evaluation. As suggested in ICCVAM's newly revised submission guidelines, nominations of promising test methods can come from various sources, including federal agencies.

Four *in vitro* ocular toxicity test methods, with potential for use in screening chemicals for severe eye irritation or corrosion, were discussed at a recent meeting, attended by EPA, of ICCVAM's advisory body, the Scientific Advisory Committee for Alternative Toxicological Methods (SACATM). These methods were identified as the Bovine Corneal Opacity and Permeability Test (BCOP), the Hen's Egg Test on Chorioallantoic Membrane (HET-CAM), the Isolated Rabbit Eye Test (IRE), and the Isolated Chicken Eye Test (ICE) or Chicken Enucleated Eye Test (CEET), which, as *in vitro* tests, may offer significant animal welfare advantages. The SACATM unanimously endorsed a recommendation that ICCVAM give high priority to performing a technical evaluation of these four test methods to assess their validation readiness, a view which the EPA understands is shared by other federal agencies with representation on ICCVAM. EPA concurs that there is merit in having ICCVAM further explore these four *in vitro* test methods on a priority basis and takes this opportunity to nominate them for a review of their validation status.

We understand that ICCVAM's process will involve preparation of a comprehensive background review document by NICEATM that will evaluate all available information (e.g. relevant existing workshop reports and published and unpublished data) and describe the current validation status of the four test methods, including what is known about their reliability and accuracy, the scope of the reference chemicals tested, and the availability of standardized protocols. A discussion in the document relating the results of the analysis of available data, as appropriate, to systems that might be used to classify eye irritation/corrosion potential (such as the globally harmonized system or those used by the European Union and United States regulatory agencies) would be helpful. The background review document would also identify the demonstrated usefulness and limitations of the methods and would be evaluated by an independent expert or peer review panel coordinated by ICCVAM and NICEATM. Such a background document and evaluation would also identify any remaining data gaps or issues concerning the validation status of each method. We understand that this would lead to the development of an ICCVAM report containing recommendations concerning the status of test method validation and identifying any test methods that are sufficiently well validated for possible regulatory acceptance.

There are several related activities that we also recommend be considered by ICCVAM. First, a review of the state of the science and the availability of *in vitro* test methods for assessing moderate or mild eye irritation, with the goal of identifying research, development and validation priorities that might advance the usefulness of such methods. Another activity is to explore ways of obtaining existing and/or of generating, if necessary, good quality *in vivo* eye irritation/corrosion reference data to assess inter-laboratory variability and support validation of *in vitro* tests. Finally, ways of alleviating pain and suffering which might arise from administration of mild to moderate irritants in current *in vivo* eye irritation testing should be explored.

We are aware that this project will call for NICEATM to engage the services of two NICEATM contract staff for one year. The EPA is willing to assist with the funding of this project, subject to Agency budget allocations, and looks forward to the opportunity to review the intended work plan should the nomination be accepted.

Sincerely,

Joseph J. Merenda, Jr.
Director
Office of Science Coordination and Policy

Cc: Jim Jones
Debra Edwards
Jack Housenger
Karen Hamernik