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Via electronic transmission to: niceatm@niehs.nih.gov

Dr. Raymond Tice
Deputy Director, NICEATM
National Institute of Environmental Health Sciences
79 T.W. Alexander Dr.
P.O. Box 12233 (MD EC-17)
Research Triangle Park, NC 27709

Re: Comments on Addendum to March 2005 Expert Panel Report on the Evaluation of the Current Validation Status of *In Vitro* Methods for Identifying Ocular Corrosives and Severe Irritants

These comments are submitted in response to a *Federal Register* notice published on November 2, 2005 (70 FR 66451) inviting public feedback regarding an addendum to the report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Expert Panel Evaluation of draft background review documents (BRDs) for four *in vitro* tests for ocular irritation and corrosion. The parties to this submission are national and international animal protection, health, and scientific advocacy organizations with a combined membership of more than 1 million Americans who share our goal of promoting reliable and relevant toxicity testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animals. These comments incorporate by reference the animal protection community's December 30, 2004 submission regarding the four ocular BRDs, as well as the composition of the expert panel charged with reviewing these documents.

The parties to this submission recognize that the *in vitro* methods currently undergoing ICCVAM review have been accepted as positive screens throughout much of Western Europe since the 1990s, and look forward to the long overdue acceptance of these methods by regulators in the United States. To this end, we are both heartened by the level of attention that these methods have received, yet also dismayed by the excessively academic nature of the ICCVAM/expert panel review. The Addendum states, for example:

> "The Panel recognized and supported the rationale for excluding some substances from the evaluation based on lack of adequate *in vivo* rabbit eye test data (i.e., severe ocular irritancy/corrosivity classification based solely on skin corrosivity, pH extremes, etc., or no classification feasible based on eye test data provided to NICEATM). While the pH and/or dermal corrosive effects of a test substance are utilized as substitutes for animal eye irritation data for the purposes of ocular hazard classification, *the goal of this evaluation was to determine whether the four in vitro test methods can be used to predict the outcome of the in vivo rabbit eye test for the same test substance*" (*emphasis supplied*).

The proper goal of any validation study should be to establish both the reliability of a test method and its relevance *to the species of ultimate concern*. Although it may indeed seem more straightforward to calculate "accuracy" and other performance parameters relative to the Draize test, it is inappropriate to treat data from a non-validated animal test as the "gold

standard" to be met by any other method(s). The Draize test has never undergone formal or adequate validation to confirm its reliability and relevance to humans (notwithstanding the recent statistical analyses by Haseman (2004) and Haseman et al. (2005) to estimate the Draize test's over- and under-classification rates for detecting ocular corrosives and severe irritants). Thus, the real-world value and utility of accuracy statistics calculated relative to Draize scores remain dubious at best, rendering the panel's decision to exclude all non-Draize data highly questionable.

We were also struck by the report that: "During the deliberations of the Panel, the question was raised as to how closely the performance of an *in vitro* test must match the performance of an *in vivo* test before the *in vitro* test is considered a sufficiently accurate measure of the risk to humans. It was acknowledged that this was an appropriate and important question to bring to ICCVAM, but one that was beyond the scope of the charge to this expert panel" (p. v). This conclusion directly contradicts the panel's stated mandate, which was to evaluate "for each of the four *in vitro* test methods, the extent and adequacy that each of the applicable ICCVAM validation and acceptance criteria … have been addressed" (Expert Panel Report: Preface, p. v.).

Finally, the Addendum states, in reference to the BCOP: "The test should not be used to identify corrosive or severely irritating ketones, alcohols, and solids. Further optimization and validation are necessary before these classes of materials can be assessed with this test" (p. 4). Regarding alcohols, we call ICCVAM's attention to BCOP and Draize/LVET data submitted by consumer product companies in relation to antimicrobial cleaning products, a number of which use alcohol-based solvents, and trust that these data have or will be taken into account to the greatest extent possible. With respect to reported difficulties in obtaining adequate historical industry data for analysis, the animal protection community is firmly committed to being an active partner in helping to overcome this barrier, and welcomes feedback regarding specific steps we could take in order to facilitate regulatory and industry acceptance of valid *in vitro* and other non-animal test methods.

Sincerely,

Troy Seidle
Director of Science Policy
People for the Ethical Treatment of Animals

Sara J. Amundson
Deputy and Legislative Director
Doris Day Animal League

Chad B. Sandusky, PhD
Director of Toxicology and Research
Physicians Committee for Responsible Medicine