DEPARTMENT OF HEALTH AND HUMAN SERVICES


**AGENCY:** Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).

**ACTION:** Request for Data; Request for Nomination of Scientific Experts

**SUMMARY:** The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), is planning to convene an independent scientific peer review panel (Panel) to assess the validation status of *in vitro* tests and integrated non-animal testing strategies proposed for identifying eye injury hazard potential of chemicals and products. On behalf of ICCVAM, NICEATM requests nominations of scientific experts who can be considered for the Panel and submission of data from substances tested in *in vitro* tests for identifying eye injury hazard potential. Of particular interest are data generated in the short-time exposure (STE) (Takahashi *et al*., 2008) and isolated rabbit eye (IRE) (ICCVAM, 2006, 2010a) tests and data from approaches using two or more *in vitro* tests. However, NICEATM requests data from other tests including, but not limited to, the bovine corneal opacity and permeability
(BCOP), isolated chicken eye (ICE), hen’s egg test – chorioallantoic membrane (HET-CAM), Cytosensor microphysiometer (CM), fluorescein leakage (FL), SkinEthic™ human corneal epithelium, and EpiOcular™ tests. If available, corresponding in vivo data for these substances are also requested, including data from any ethical human or animal studies or accidental human exposures.

**DATES:** Nominations and test method data for the STE and IRE tests should be submitted by [insert date 45 days from publication]. Data submitted after this date will be considered in the evaluation where feasible.

**FOR FURTHER INFORMATION CONTACT:** Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2–16, Research Triangle Park, NC, 27709, (telephone) 919–541–2384, (fax) 919–541–0947, (email) niceatm@niehs.nih.gov. Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

**SUPPLEMENTARY INFORMATION:**

**Background**

The development of in vitro alternatives to animals for eye safety assessments is an ICCVAM priority (ICCVAM, 2008). See [http://iccvam.niehs.nih.gov/methods/ocutox/ocutox.htm](http://iccvam.niehs.nih.gov/methods/ocutox/ocutox.htm) for more information on ICCVAM evaluations of ocular toxicity test methods. An efficient non-animal evaluation of substances for their eye hazard potential is expected to require a number of adequately validated in vitro tests that can be considered for use in integrated testing and decision strategies. In vivo reference data and in vitro test data for available methods is sought to support the validity of individual methods and to construct integrated testing
and decision strategies using multiple methods.

In 2006, ICCVAM evaluated the validation status of the *in vitro* tests BCOP, ICE, HET-CAM, and IRE for their usefulness and limitation for identifying ocular corrosives and severe irritants (ICCVAM, 2006). ICCVAM concluded that BCOP and ICE had sufficient relevance and reliability to support their use for identifying certain types of substances as ocular corrosives and severe irritants for regulatory hazard classification. Subsequently, BCOP and ICE were adopted as Organisation for Economic Co-operation and Development (OECD) Test Guidelines 437 and 438, respectively (OECD, 2009a, 2009b). The IRE and HET-CAM tests lacked sufficient data and/or had insufficient relevance and reliability to support their use for regulatory hazard classification.

In 2009, ICCVAM evaluated the validation status of these four *in vitro* tests for identifying eye injury hazard potential, along with the CM test, to assess their usefulness for identifying nonsevere eye irritants and substances not classified as irritants (ICCVAM, 2010a). ICCVAM concluded that the CM test could be used as a screening test to identify some types of substances that may cause permanent or severe eye injuries. ICCVAM also recommended that the CM test could be used to determine if some types of substances will not cause sufficient injury to require hazard classification for eye irritation. The predictivity of the remaining four *in vitro* tests was considered insufficient to support their use for identifying substances that may cause reversible and nonsevere eye injuries.

ICCVAM also evaluated the validation status of the antimicrobial cleaning products (AMCP) testing strategy, which included the BCOP, CM, and EpiOcular™ tests. ICCVAM concluded that the data were insufficient to adequately demonstrate that
the AMCP testing strategy can identify all four U.S. Environmental Protection Agency (EPA) eye hazard categories (ICCVAM, 2010b). An EPA-implemented voluntary pilot program is ongoing to evaluate the use of the AMCP testing strategy for eye irritation labeling for certain antimicrobial products (http://www.epa.gov/oppad001/eye-irritation.pdf).

The IRE test is an organotypic test method that evaluates the eye injury potential of a test substance by measuring corneal opacity, corneal swelling, epithelial integrity, and fluorescein staining. During the previous evaluations of the IRE test, ICCVAM recommended further standardization of the test protocol and additional studies using all four endpoints to expand the IRE test validation database (ICCVAM, 2006, 2010a).

The STE test measures the viability of rabbit corneal epithelial cells following test substance exposure (Takahashi et al., 2008). NICEATM is requesting additional data that can be considered in assessing the validity of the STE and the IRE. Other test methods and integrated testing and decision strategies will also be considered for review if there are sufficient new data available.

For test methods and strategies for which there are sufficient data, ICCVAM will develop draft recommendations on test method usefulness and limitations, standardized test method protocols, future studies that may expand the usefulness of the test method, and test method performance standards. These draft recommendations and supporting data will be provided to the Panel and made available to the public. The Panel will meet in public session to review the validation status of the proposed methods and comment on the extent to which the data support the draft ICCVAM test method recommendations. Meeting information, including dates, locations, and public availability of the meeting
documents will be announced in a future Federal Register notice and will also be posted on the NICEATM–ICCVAM website (http://iccvam.niehs.nih.gov).

Request for Nominations of Scientific Experts

NICEATM requests nominations of scientists with relevant knowledge and expertise to serve on the Panel. Areas of relevant expertise include, but are not limited to biostatistics; human and veterinary ophthalmology, with an emphasis on evaluation and treatment of chemical injuries; in vivo eye safety testing; in vitro eye safety testing; and test method validation. Each nomination should include the nominee’s name, affiliation, contact information (i.e., mailing address, email address, telephone and fax numbers), curriculum vitae, and a brief summary of relevant experience and qualifications.

Request for Data

NICEATM invites the submission of data from substances tested in any in vitro test and integrated non-animal testing strategies proposed for identifying eye injury hazard potential of chemicals and products. If available, in vivo reference data for substances tested in these data sets are also requested. Although data can be accepted at any time, please submit data by [insert date 45 days from publication] to ensure consideration during the ICCVAM evaluation process. Relevant data received after this date will be considered where feasible. All information submitted in response to this notice will be made publicly available and may be incorporated into future NICEATM and ICCVAM reports and publications, as appropriate.

When submitting data, please reference this Federal Register notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, email, and sponsoring organization, as applicable). NICEATM prefers that data be submitted as
copies of pages from study notebooks and/or study reports, if available. Laboratory data and analyses available in electronic format may also be submitted. Each submission for a substance should preferably include the following information, as appropriate: common and trade name, Chemical Abstracts Service Registry Number (CASRN), commercial source, in vitro test protocol used, rabbit eye test protocol used, individual animal or in vitro responses at each observation time (i.e., raw data), extent to which the data were collected in accordance with national or international Good Laboratory Practice guidelines, date and testing organization, and physical and chemical properties (e.g., molecular weight, pH, water solubility, etc.)

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods and integrated testing strategies with regulatory applicability and promotes the scientific validation and regulatory acceptance of testing methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine (enhance animal well-being and lessen or avoid pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM welcome the public nomination of new, revised,
and alternative test methods and strategies for validation studies and technical evaluations. Additional information about NICEATM and ICCVAM can be found on the NICEATM–ICCVAM website (http://iccvam.niehs.nih.gov).

References


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John R. Bucher, Ph.D.
Associate Director, National Toxicology Program

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