
**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

**National Toxicology Program (NTP);
NTP Interagency Center for the
Evaluation of Alternative Toxicological
Methods (NICEATM); Availability of
Interagency Coordinating Committee
on the Validation of Alternative
Methods (ICCVAM) Test Method
Evaluation Reports: In Vitro Ocular
Safety Testing Methods and Strategies,
and Routine Use of Topical
Anesthetics, Systemic Analgesics, and
Humane Endpoints for Ocular Safety
Testing; Notice of Transmittal to
Federal Agencies**

AGENCY: National Institute of
Environmental Health Sciences
(NIEHS), National Institutes of Health
(NIH).

ACTION: Availability of ICCVAM Test
Method Evaluation Reports (TMERs);
Notice of Transmittal.

SUMMARY: NICEATM announces
availability of ICCVAM TMERs that
provide recommendations regarding
proposed *in vitro* ocular safety testing
methods, testing strategies, and the
routine use of anesthetics, analgesics,
and humane endpoints for ocular safety
testing to avoid or minimize any pain
and distress. The reports and
recommendations have been transmitted
to Federal agencies for their review and
response to ICCVAM in accordance with
the ICCVAM Authorization Act of 2000.
In the first report, ICCVAM recommends
pain management procedures that
should always be used to avoid or
minimize pain and distress when it is
determined necessary to conduct the

rabbit eye test for regulatory safety purposes. In the second report, ICCVAM recommends that the Cytosensor microphysiometer (CM) test method can be used as a screening test to identify some types of substances that may cause permanent or severe eye injuries. ICCVAM also recommends that the CM test method can be used to determine if some types of substances will not cause sufficient injury to require hazard labeling for eye irritation. ICCVAM evaluated four other *in vitro* test methods for their usefulness and limitations for identifying substances with the potential to cause reversible and nonsevere ocular injuries, but concluded that the performance of these methods must be improved before they can be used for regulatory safety testing to classify such substances. The report includes ICCVAM recommendations for future studies that could potentially improve these test methods. In the third report, ICCVAM recommends further studies to characterize the usefulness and limitations of a non-animal *in vitro* testing strategy that uses three *in vitro* test methods. In the fourth report, ICCVAM recommends that a proposed low volume rabbit eye test (LVET) should not be used for regulatory testing due to performance issues when compared to the current standard rabbit eye test.

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, (e-mail) niceatm@niehs.nih.gov. Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

SUPPLEMENTARY INFORMATION:

Background

In October 2003, the U.S. Environmental Protection Agency (EPA) requested ICCVAM to: (1) Evaluate the current validation status of the bovine corneal opacity and permeability (BCOP), hen's egg test-chorioallantoic membrane (HET-CAM), isolated chicken eye (ICE), and isolated rabbit eye (IRE) test methods; (2) identify *in vivo* ocular toxicity reference data to support the validation of *in vitro* test methods; (3) explore ways of alleviating pain and suffering from current *in vivo* ocular safety testing; and (4) review the state of the science and the availability of *in vitro* test methods for assessing mild or moderate ocular irritants. The highest priority activity, an evaluation of the BCOP, HET-CAM, ICE, and IRE test methods for their ability to identify potential ocular corrosives, was

completed in 2006 (NIH Publication No. 07-4517; available at http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox/ocu_tmer.htm). ICCVAM recently completed additional test method evaluations relevant to the original EPA nomination and a subsequent EPA request for ICCVAM to evaluate a proposed *in vitro* testing strategy for identifying the ocular hazard potential of antimicrobial cleaning products (AMCPs).

NICEATM and ICCVAM compiled comprehensive draft background review documents (BRDs) and released them for public comment in March 2009 (74 FR 14556). ICCVAM convened a public panel meeting on May 19-21, 2009, to review the draft documents and assess whether the information they contained supported draft ICCVAM test method recommendations for test method uses and limitations, updated standardized test method protocols, and proposed future studies. The panel considered public comments made at the meeting as well as public comments submitted in advance of the meeting before concluding its deliberations. The panel's report was made available in July 2009 (74 FR 33444) for public comment. The draft ICCVAM BRDs, draft ICCVAM test method recommendations, the panel's report, and all public comments were made available to ICCVAM's Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) for comment at its meeting on June 25-26, 2009 (74 FR 19562).

After considering the conclusions and recommendations of the panel, comments from SACATM, and public comments, ICCVAM forwarded final test method recommendations to U.S. Federal agencies for their consideration. Agency responses to the ICCVAM test method recommendations will be made available on the NICEATM-ICCVAM Web site (<http://www.iccvam.niehs.nih.gov>) as they are received.

The ICCVAM TMER, *Recommendations for Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints to Avoid or Minimize Pain and Distress in Ocular Safety Testing* (NIH Publication No. 10-7514) provides ICCVAM's evaluation and recommendations for the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing. ICCVAM concludes that balanced preemptive pain management procedures should always be provided when it is determined necessary to conduct the rabbit eye test for regulatory

safety assessments. ICCVAM also identifies clinical signs and ocular lesions that are considered predictive of an ocular corrosive or severe irritant response and, therefore, can be routinely used as humane endpoints to end studies early when deemed appropriate. The report also includes a test method protocol that incorporates the ICCVAM-recommended procedures, the final BRD, and the panel's peer review report.

The ICCVAM TMER, *Current Validation Status of In Vitro Test Methods Proposed for Identifying Eye Injury Hazard Potential of Chemicals and Products* (NIH Publication No. 10-7553) provides ICCVAM's updated evaluation and recommendations for the use of five *in vitro* ocular test methods (*i.e.*, BCOP, CM, HET-CAM, ICE, and IRE) for their ability to identify nonsevere ocular irritants and substances not labeled as irritants. ICCVAM concludes that the CM test method can be used as a screening test to identify test substances within a defined limited applicability domain that may cause permanent or severe eye injuries. ICCVAM also recommends that the CM can be used to determine if substances within an even more restricted applicability domain will not cause sufficient injury to require hazard labeling for eye irritation. The performance of the remaining four *in vitro* test methods must be improved before they can be used in regulatory safety testing for classifying substances not labeled as irritants. None of these *in vitro* test methods were considered adequately predictive of all ocular hazard categories to support their use as a complete replacement for the current standard rabbit eye test. This report also includes updated ICCVAM-recommended BCOP, CM, HET-CAM, ICE, and IRE test method protocols, final BRDs for the BCOP, CM, HET-CAM, and ICE test methods, and the panel's peer review report.

ICCVAM also discovered during these evaluations that an estimated 30% of chemicals identified as eye hazards by current U.S. regulations will not be labeled as eye hazards by the United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS), which some Federal agencies are or will be considering for implementation. The reduced hazard labeling that will result from implementing the GHS was based on analyzing actual testing data for over 250 chemicals. Of concern is that over 50% of the chemicals that will no longer be labeled using GHS criteria produced eye injuries expected to interfere with normal vision. Accordingly, the report

includes an optional GHS hazard category that could be used to provide at least equivalent hazard labeling as current U.S. regulations in order to support continued protection of consumers and workers.

The ICCVAM TMER, *Current Validation Status of a Proposed In Vitro Testing Strategy for U.S. Environmental Protection Agency Ocular Hazard Classification and Labeling of Antimicrobial Cleaning Products* (NIH Publication No. 10-7513) provides ICCVAM's evaluation and recommendations regarding the use of a proposed in vitro testing strategy to classify and label AMCPs for eye irritation. ICCVAM concludes that the data are insufficient to adequately demonstrate that the proposed *in vitro* testing strategy can classify test substances to all four EPA ocular hazard categories. ICCVAM recommends further studies to characterize the usefulness and limitations of the non-animal *in vitro* testing strategy that uses the three in vitro test methods. This report also includes updated ICCVAM-recommended BCOP, CM, and EpiOcular™ test method protocols, the final summary review document (SRD), and the panel's peer review report.

The ICCVAM TMER, *Recommendation to Discontinue Use of the Low Volume Eye Test for Ocular Safety Testing* (NIH Publication No. 10-7515) provides ICCVAM's evaluation and recommendations on the usefulness of the LVET as an *in vivo* reference test method. ICCVAM concludes that the proposed LVET should not be used for regulatory safety testing due to performance issues.

Background Information on ICCVAM, NICEATM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, or generate toxicological and safety testing information for chemicals, products, and other substances. ICCVAM conducts technical evaluations of new, revised, and alternative methods with regulatory applicability, and promotes the scientific validation and regulatory acceptance of toxicological and safety testing methods that more accurately assess the safety and health hazards of chemicals and products while reducing, refining (decreasing or eliminating pain and distress), or replacing animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 2851-2, 2851-5 [2000]), available at http://iccvam.niehs.nih.gov/docs/about_docs/PL106545.pdf 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 coordinates international validation studies of new and improved test methods. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of U.S. Federal agencies. NICEATM and ICCVAM welcome the public nomination of new, revised, and alternative test methods for validation studies as well as technical evaluations. Additional information about NICEATM and ICCVAM can be found on the NICEATM-ICCVAM Web site (<http://www.iccvam.niehs.nih.gov>).

SACATM was established January 9, 2002, and is composed of scientists from the public and private sectors (67 FR 11358). SACATM provides advice to the Director of the NIEHS, ICCVAM, and NICEATM regarding the statutorily mandated duties of ICCVAM and activities of NICEATM. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at <http://ntp.niehs.nih.gov/go/167>.

References

- ICCVAM. 2006. ICCVAM Test Method Evaluation Report: In Vitro Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives. NIH Publication No. 07-4517. Research Triangle Park, NC: NIEHS. Available: http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox/ocu_tmer.htm.
- ICCVAM. 2010. ICCVAM Test Method Evaluation Report: Recommendations for Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints to Avoid or Minimize Pain and Distress in Ocular Safety Testing. NIH Publication No. 10-7514. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/OcuAnest-TMER.htm>.
- ICCVAM. 2010. ICCVAM Test Method Evaluation Report: Current Validation Status of In Vitro Test Methods Proposed for Identifying Eye Injury Hazard Potential of Chemicals and Products. NIH Publication No. 10-7553. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/MildMod-TMER.htm>.
- ICCVAM. 2010. ICCVAM Test Method Evaluation Report: Current Validation Status of a Proposed In Vitro Testing Strategy for U.S.

Environmental Protection Agency Ocular Hazard Classification and Labeling of Antimicrobial Cleaning Products. NIH Publication No. 10-7513. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/AMCP-TMER.htm>.

ICCVAM. 2010. ICCVAM Test Method Evaluation Report: Recommendation to Discontinue Use of The Low Volume Eye Test for Ocular Safety Testing. NIH Publication No. 10-7515. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/LVET.htm>.

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