
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Recommendations on In Vitro Ocular Safety Testing Methods and Strategies and Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints for Ocular Safety Testing

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

ACTION: Notice of availability.

SUMMARY: U.S. Federal agency responses to ICCVAM test method recommendations on alternative testing methods and strategies proposed to further reduce and refine the use of animals for assessing the ocular hazard potential of chemicals and products are now available. ICCVAM recommended a pain management procedure that should always be used to avoid pain and distress when it is determined necessary to conduct the rabbit eye test for regulatory safety purposes. ICCVAM also recommended the Cytosensor Microphysiometer (CM) test method as a screening test (1) to identify some types of substances that will not cause sufficient injury to require eye hazard labeling and (2) to identify some types of substances that may cause permanent or severe eye injuries. ICCVAM previously forwarded recommendations to Federal agencies and made these recommendations available to the public (75 FR 57027). In accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*–3), agencies have notified ICCVAM in writing of their findings and ICCVAM is making these responses available to the public. Federal agency responses are available on the NICEATM–ICCVAM Web site at *http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm.* The ICCVAM recommendations are provided in ICCVAM test method evaluation reports that are available on the NICEATM–ICCVAM Web site at *http://iccvam.niehs.nih.gov/methods/ocutox/OcuAnest-TMER.htm, http://iccvam.niehs.nih.gov/methods/ocutox/MildMod-TMER.htm, http://iccvam.niehs.nih.gov/methods/ocutox/AMCP–TMER.htm,* and *http://iccvam.niehs.nih.gov/methods/ocutox/LVET.htm.*

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

The U.S. Environmental Protection Agency (EPA) requested that ICCVAM (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 distress 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 usefulness and limitations for identifying potential ocular corrosives and severe irritants, was completed in 2006 (NIH Publication No. 07–4517). Based on this evaluation, U.S. Federal agencies subsequently accepted the BCOP and ICE test methods for certain regulatory testing purposes without the need for animal testing. The Organisation for Economic Co-operation and Development (OECD) subsequently adopted the BCOP and ICE test methods in 2009 as international OECD Test Guidelines 437 and 438, respectively (OECD 2009a, OECD 2009b). The International Organization for Standardization (ISO) adopted the BCOP and ICE test methods as ISO Standard 10993–10 in 2010 (ISO 2010).

ICCVAM recently completed additional test method evaluations relevant to the original EPA nomination and a subsequent EPA request that ICCVAM evaluate a proposed in vitro testing strategy for identifying the ocular hazard potential of antimicrobial cleaning products. Information is provided about ICCVAM's evaluation and the committee's recommendations for the alternative testing methods and strategies proposed to further reduce and refine the use of animals for assessing the ocular hazard potential of chemicals and products in four ICCVAM Test Method Evaluation Reports: (1) *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), (2) *Current Validation Status of In Vitro Test Methods Proposed for Identifying Eye Injury Hazard Potential of Chemicals and Products* (NIH Publication No. 10–7553), (3) *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), and (4) *Recommendation to Discontinue Use of the Low Volume Eye Test for Ocular Safety Testing* (NIH Publication No. 10–7515).

Agency Responses to ICCVAM Recommendations

In September 2010, ICCVAM forwarded final test method recommendations for ocular safety testing methods and strategies to U.S. Federal agencies for consideration, in accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C.

285*l*–3) (75 FR 57027). The ICCVAM Authorization Act requires member agencies to review ICCVAM test method recommendations and notify ICCVAM in writing of their findings no later than 180 days after receipt of recommendations. The Act also requires ICCVAM to make ICCVAM recommendations and agency responses available to the public. Agency responses should include identification of relevant test methods for which the ICCVAM test method recommendations may be added or substituted and indicate any revisions or planned revisions to existing guidelines, guidances, or regulations to be made in response to these recommendations.

ICCVAM agencies concurred with the test method recommendations for the in vitro ocular safety testing methods and strategies and support the routine use of topical anesthetics, systemic analgesics, and humane endpoints for ocular safety testing. Several agencies also indicated that they would communicate the ICCVAM recommendations to stakeholders and encourage their appropriate use. Agency responses are available at *http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm.*

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 with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological and safety testing methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine (decrease or eliminate pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*–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 work collaboratively to evaluate new and improved test methods and strategies applicable to the needs of U.S. Federal agencies. 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 ICCVAM and NICEATM can be found on the NICEATM–ICCVAM Web site (*http://iccvam.niehs.nih.gov*).

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.*

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OECD. 2009a. Test Guideline 437. Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants, adopted September 2009. In: OECD Guidelines for Testing of Chemicals. Paris: OECD. Available: *http://www.oecd-ilibrary.org/environment/test-no-437-bovine-corneal-opacity-and-permeability-test-method-for-identifying-ocular-corrosives-and-severe-irritants_9789264076303-en.*

OECD. 2009b. Test Guideline 438. Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants, adopted September 2009. In: OECD Guidelines for Testing of Chemicals. Paris: OECD. Available: *http://www.oecd-ilibrary.org/environment/test-no-438-isolated-chicken-eye-test-method-for-identifying-ocular-corrosives-and-severe-irritants_9789264076310-en.*

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John R. Bucher,

Associate Director, National Toxicology Program.

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