

Review of Alternative Test Methods and Integrated Strategies for Ocular Safety Assessments

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U.S. FDA

ICCVAM Best Practices Workshop

William H. Natcher Conference Center
National Institutes of Health
Bethesda, MD

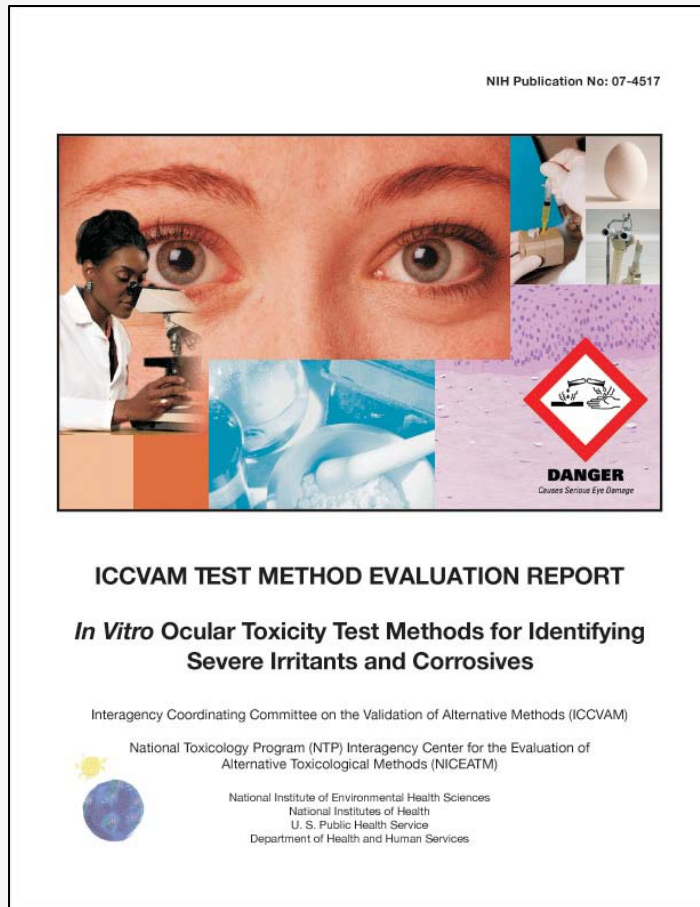
January 19, 2011



Outline

- Introduction
- Overview of ICCVAM evaluation, recommendations, and Agency responses for available alternative methods for ocular safety testing
 - Bovine Corneal Opacity and Permeability (BCOP) test method
 - Isolated Chicken Eye (ICE) test method
 - Cytosensor™ Microphysiometer (CM) test method
 - Routine use of analgesics, anesthetics, and humane endpoints in required *in vivo* ocular safety testing
- Integrated decision strategies for ocular safety assessments

ICCVAM Evaluation and Recommendations for BCOP and ICE



ICCVAM. 2006. NIH Publication No. 07-4517. RTP, NC:NIEHS. Available: http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox/ocu_tmer.htm

- Submitted to ICCVAM in 2003 by U.S. EPA
- ICCVAM International Peer Review Panel Meeting (2005)
- Evaluated four alternative test methods for identifying severe irritants and corrosives
 - BCOP
 - HET-CAM
 - ICE
 - IRE
- ICCVAM test method evaluation report and recommendations published November 2006
 - Based on the validation database and performance, positive results in the BCOP and ICE test methods can be used to identify ocular corrosives and severe irritants without the need for animal testing

Regulatory Acceptance of BCOP and ICE

- ICCVAM recommendations accepted by U.S. Federal regulatory agencies in 2008
- OECD TGs adopted 2009
 - OECD TG 437 (BCOP)
 - OECD TG 438 (ICE)
- International Organization for Standardization (ISO) Inclusion
 - ISO 10993-10:2010 Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization

OECD/OCDE 437
Adopted:
7 September 2009

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

OECD/OCDE 438
Adopted:
7 September 2009

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants

ICCVAM Peer Review Panel Meeting (2009)



NICEATM
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM
Interagency Coordinating Committee on the Validation of Alternative Methods

**INDEPENDENT SCIENTIFIC
PEER REVIEW PANEL MEETING**

**Evaluation of the Validation Status of Alternative
Ocular Safety Testing Methods and Strategies**

- Using topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress
- The low volume in vivo eye test
- Four in vitro test methods to identify moderate, mild, and nonlabeled ocular irritant categories
- In vitro strategy to assess the eye irritation potential of antimicrobial cleaning products

May 19-21, 2009
Consumer Product Safety Commission
Headquarters - Bethesda, MD

For more information and to register, please contact NICEATM:
<http://iccvam.niehs.nih.gov/>
919-541-2352
nicvatm@niehs.nih.gov

ICCVAM Agencies:

• Agency for Toxic Substances and Hazard Registry	• National Institutes of Health
• Consumer Product Safety Commission	• National Cancer Institute
• Department of Agriculture	• National Institute of Environmental Health Sciences
• Department of Defense	• National Institute for Occupational Safety and Health
• Department of Energy	• National Library of Medicine
• Department of the Interior	• Occupational Safety and Health Administration
• Department of Transportation	
• Environmental Protection Agency	
• Food and Drug Administration	



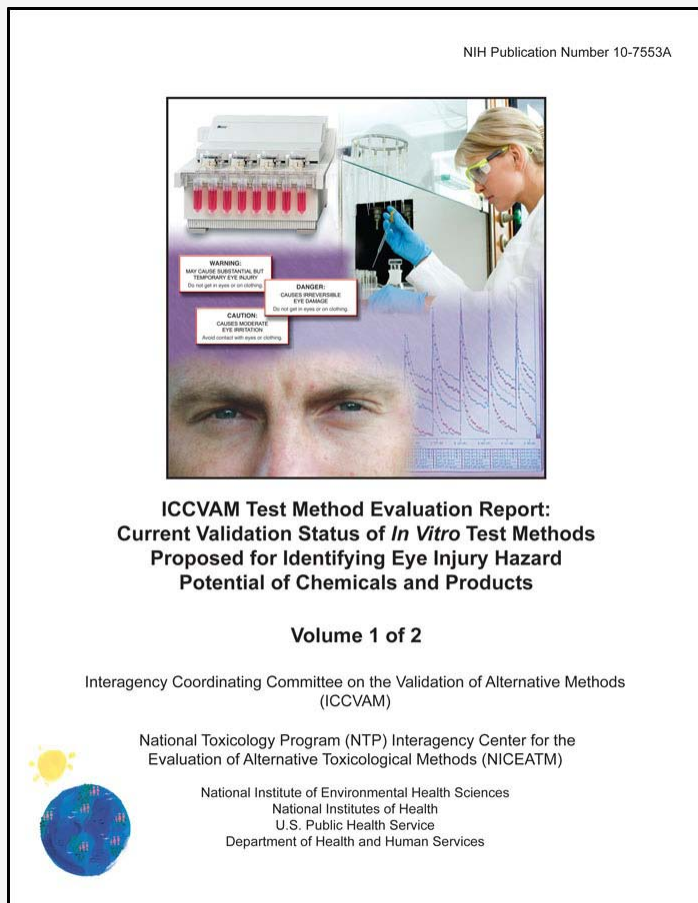
- International Public Peer Review Panel Meeting
 - 22 experts from 6 countries
 - Considered draft background review documents and draft ICCVAM recommendations
- Evaluated 10 alternative test methods and strategies, including
 - CM
 - Routine use of systemic analgesics, topical anesthetics, and humane endpoints

ICCVAM. 2009. Available:

http://iccvam.niehs.nih.gov/docs/ocutox_docs/OcularPRPRept2009.pdf

NICEATM-ICCVAM: Advancing Public Health and Animal Welfare

ICCVAM Evaluation and Recommendations: CM

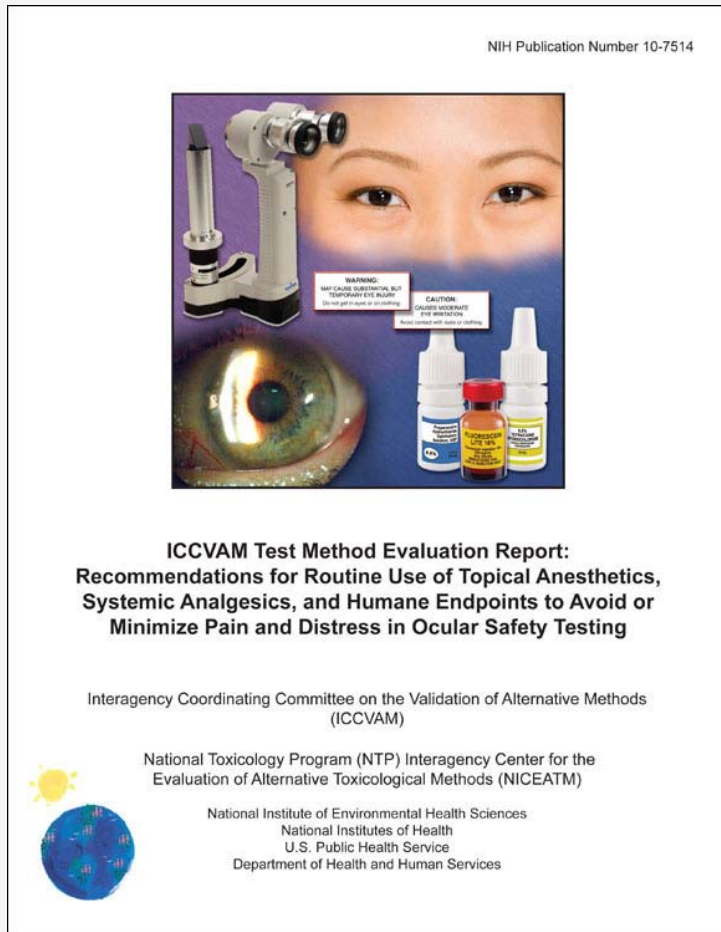


ICCVAM. 2010. NIH Publication No. 10-7553A. RTP, NC NIEHS.
Available:
<http://iccvam.niehs.nih.gov/methods/ocudocs/MildMod-TMER.htm>

- ICCVAM test method evaluation report and recommendations published September 2010
 - Based on the validation database and performance, positive results in the CM can be used for substances within a defined limited applicability domain to identify ocular corrosives and severe irritants without the need for animal testing
 - Negative results in the CM can also be used for substances within an even more restricted applicability domain to identify substances not labeled as irritants without the need for animal testing

- Federal agency responses due to ICCVAM March 7, 2011
 - Many available now

ICCVAM Evaluation and Recommendations: Topical Anesthetics, Systemic Analgesics, and Humane Endpoints



ICCVAM. 2010. NIH Publication No. 10-7514. RTP, NC:NIEHS.
Available: <http://iccvam.niehs.nih.gov/methods/ocutox/OcuAnest-TMER.htm>

- ICCVAM test method evaluation report and recommendations published September 2010
 - A balanced preemptive pain management plan should *always* be used when the rabbit eye test is conducted for regulatory safety testing
 - Additional humane endpoints that should be used to end studies earlier
- Federal agency responses due to ICCVAM March 7, 2011
 - Many available now

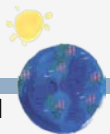
Summary of ICCVAM Evaluations

- BCOP and ICE are now available for use internationally with the adoption of OECD TGs 437 (BCOP) and 438 (ICE) and reference to their availability and use in ISO 10993-10
- The CM, pending U.S. agency acceptance, will be the first *in vitro* test method that can be used, with specified limitations, to identify substances not labeled as irritants
- Appropriate use of the ICCVAM-recommended BCOP, ICE, and CM protocols are expected to support both continued protection of public health and improved animal welfare
- Use of these tests in a tiered testing strategy should refine and reduce use of the rabbit eye test
 - Where applicable for identification of corrosives and severe irritants and/or substances not labeled as irritants
- Use of anesthetics, analgesics, and humane endpoints in the rabbit eye test, pending U.S. agency acceptance, will further refine the use of the rabbit eye test

Integrated Sequential Testing Strategy for Potential Ocular Hazards¹ (1)

1. Evaluate existing human and/or animal data on eyes and skin
 - If show effects on eyes or corrosive/severe irritant effects on skin, assume corrosive or irritating to eyes – no testing is needed
 - **OR:** If no information available or available information is not conclusive, go to step 2
2. Perform structure activity relationships (SAR)
 - If predict effects on eyes or skin corrosivity, assume corrosive or irritating to eyes – no testing is needed
 - **OR:** If no predictions can be made or predictions are not conclusive or negative, go to step 3
3. Measure pH (buffering capacity, if relevant)
 - If $\text{pH} \leq 2.0$ or ≥ 11.5 with high buffering capacity, assume corrosivity to eyes – no testing is needed
 - **OR:** If $2 < \text{pH} < 11.5$ or $\text{pH} \leq 2.0$ or ≥ 11.5 with low/no buffering capacity, go to step 4
4. Evaluate systemic toxicity via the dermal route
 - If highly toxic at concentrations that would be tested in the eye, substance too toxic for testing – no testing is needed
 - **OR:** If such information is not available or substance is not highly toxic, go to step 5

¹ Modified from TG 405 (OECD 2002)



Integrated Sequential Testing Strategy for Potential Ocular Hazards¹ (2)

5. Perform validated and accepted *in vitro* or *ex vivo* test for eye corrosion
 - If corrosive response, assume corrosivity to eyes – no further testing is needed
 - **OR:** If substance is not corrosive or a validated and accepted *in vitro* or *ex vivo* test for eye corrosion is not yet available, go to step 6
6. Perform validated and accepted *in vitro* or *ex vivo* test for eye irritation
 - If irritant response, assume irritancy to eyes – no further testing is needed
 - **OR:** If substance is not an irritant or a validated and accepted *in vitro* or *ex vivo* test for eye irritation is not yet available, go to step 7
7. Experimentally assess *in vivo* skin irritation/corrosion potential (TG 404)
 - If corrosive or severe irritant response, assume corrosivity to eyes – no further testing is needed
 - **OR:** If substance is not corrosive or severely irritating to skin, go to step 8
8. Perform initial *in vivo* rabbit eye test using one animal
 - If severe damage to eyes, consider corrosive to eyes – no further testing is needed
 - **OR:** If no severe damage or no response, go to step 9

¹ Modified from TG 405 (OECD 2002)

Integrated Sequential Testing Strategy for Potential Ocular Hazards¹ (3)

9. Perform confirmatory test using one or two additional animals
 - If corrosive or irritating, consider corrosive or irritating to eyes – no further testing is needed
 - **OR:** If not corrosive or irritating, consider non-irritating and non-corrosive to eyes – no further testing is needed

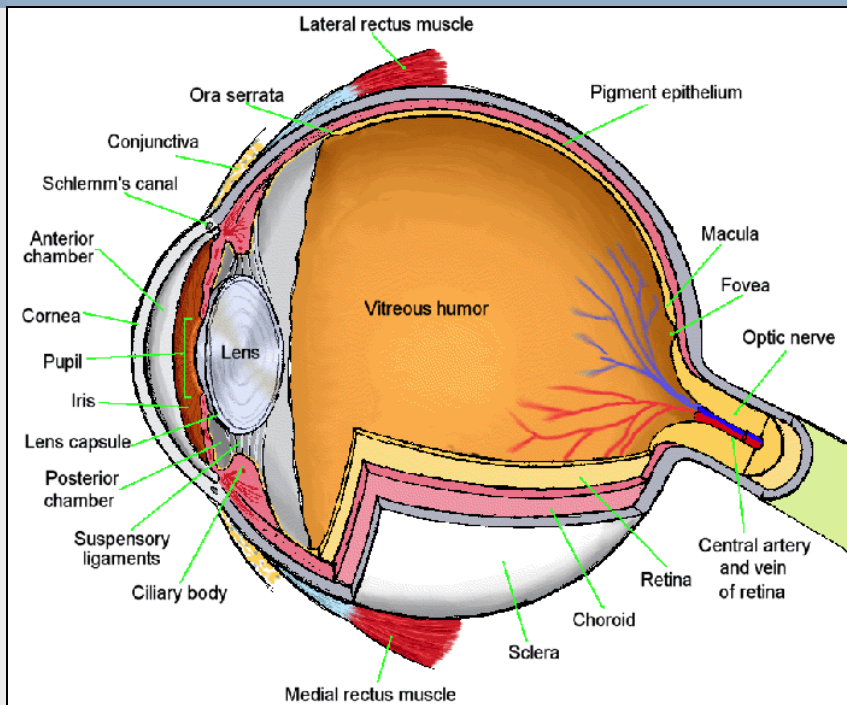
¹ Modified from TG 405 (OECD 2002)

Use of Alternative Methods in Integrated Strategies for Ocular Safety Assessments

- Some alternative methods may have a range of responses that are associated with an unacceptable level of uncertainty and that cannot, therefore, be used alone for hazard decisions
- Additional information or data could be used to reduce the uncertainty associated with these results using an integrated strategy to reach a hazard decision
- Integrated strategies using multiple sources of data and information can increase the certainty of hazard decisions beyond the certainty associated with only a single source of data or information
- Important to include test methods that incorporate key pathway events in eye irritation/corrosion

Source: Stokes WS, Wind M. 2010. Validation of innovative technologies and strategies for regulatory safety assessment methods: challenges and opportunities. *ALTEX* 27:87-95.

Integrated Strategies: Consideration of Key Pathway Events in Eye Irritation/Corrosion



Histology image © Mission for Vision. Available: <http://www.images.missionforvisionusa.org/anatomy/2005/10/cornea-histology.html>

- Damage to corneal structures resulting in:
 - Opacity
 - Swelling (chemosis)
 - Cell death with apoptosis and/or necrosis
 - Ulceration
 - Scarring
- Inflammation
 - Release of inflammatory mediators
 - Release of pain mediators
 - Cell proliferation and migration
 - Stromal collagen reorganization
- Depth of Injury
 - Epithelium - 1
 - Bowman's layer - 2
 - Stroma - 3
 - Descemet's membrane - 4
 - Endothelium - 5

Integrated Strategies for Ocular Safety Assessments: Summary

- BCOP and ICE can be used in a tiered testing strategy, with specified limitations and applicability, to screen and identify ocular corrosives and severe irritants that otherwise would be tested in the rabbit eye test, thereby contributing to reduced animal use
- CM can be used in a tiered testing strategy, with specified limitations and applicability, to screen and identify substances not labeled as irritants and/or ocular corrosives and severe irritants
- New methods in the validation pipeline will further improve integrated strategies and are expected to increasingly replace the use of animals for ocular safety testing
 - EpiOcular™ and SkinEthic™ test methods - ECVAM Eye Irritation Validation Study
 - Fluorescein leakage test method
 - Antimicrobial Cleaning Product testing strategy pilot program
 - Isolated rabbit eye test method
 - Short time exposure test method - JaCVAM Validation Study
 - ***More on these methods later today***

Eye Injury Regulatory Safety Testing Workshop: Goals

- Review available methods: applications, strengths, and weaknesses
- Provide procedures for conducting and interpreting data in accordance with regulatory testing requirements and guidelines
- Become familiar with data generated by each test method
- Share information on the appropriate use of results in regulatory safety testing
- Discuss challenges
- Identify and discuss new methods
- Solicit high quality data for validating new methods



ICCVAM Workshop Series on Best Practices for Regulatory Safety Testing:

- *January 19, 2011: Assessing the Potential for Chemically Induced Eye Injuries*
- *January 20, 2011: Assessing the Potential for Chemically Induced Allergic Contact Dermatitis*

Two one-day workshops on available alternative methods that evaluate hazard potential of chemicals and products, minimize animal use, and avoid animal pain and distress.

William H. Natcher Conference Center
National Institutes of Health — Bethesda, MD, USA

Organized by: NICEATM - National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
ICCVAM - Interagency Coordinating Committee on the Validation of Alternative Methods

The workshop is open to the public with no registration fee.
For more information and to register, please contact NICEATM:
website: <http://iccvam.niehs.nih.gov>
phone: 919-541-2384 email: niceatm@niehs.nih.gov

ICCVAM Agencies:

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• Consumer Product Safety Commission	• Department of Transportation	• NIH Office of the Director
• Department of Agriculture	• Environmental Protection Agency	• National Library of Medicine
• Department of Defense	• Food and Drug Administration	• Occupational Safety and Health Administration
• Department of Energy	• National Cancer Institute	
	• National Institute of Environmental Health Sciences	





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¹ Could not attend the Panel meeting, but agreed to participate in the review of all materials

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