

ICCVAM Evaluation and Recommendations on Best Practices for Incorporating Pain Management and Humane Endpoints in Ocular Safety Testing

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National Institutes of Health
Bethesda, MD**

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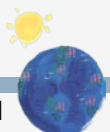


Outline

- Background
- ICCVAM Recommendations
 - Routine use of topical anesthetics and systemic analgesics
 - Pain management procedures for *in vivo* ocular safety testing
 - Routine use of humane endpoints
 - Changes to ocular safety testing protocols

Current Guidance on Minimizing Pain and Distress in Ocular Safety Testing (1)

- Use of topical anesthetics and systemic analgesics:
 - Current EPA and OECD test guidelines for the rabbit eye test provide for the use of topical anesthetics *only when the user demonstrates that such pretreatments do not interfere with the test results* (EPA 2003; OECD 2002)
 - However, since 1984 the U.S. Consumer Product Safety Commission (CPSC) has recommended pre-application of tetracaine ophthalmic anesthetic for all rabbit eye toxicity studies
 - No reference to the use of any post-application use of pain relieving medications
 - *“Animals showing continuing signs of severe distress and/or pain at any stage of the test should be humanely killed, and the substance assessed accordingly”* (OECD 2002).

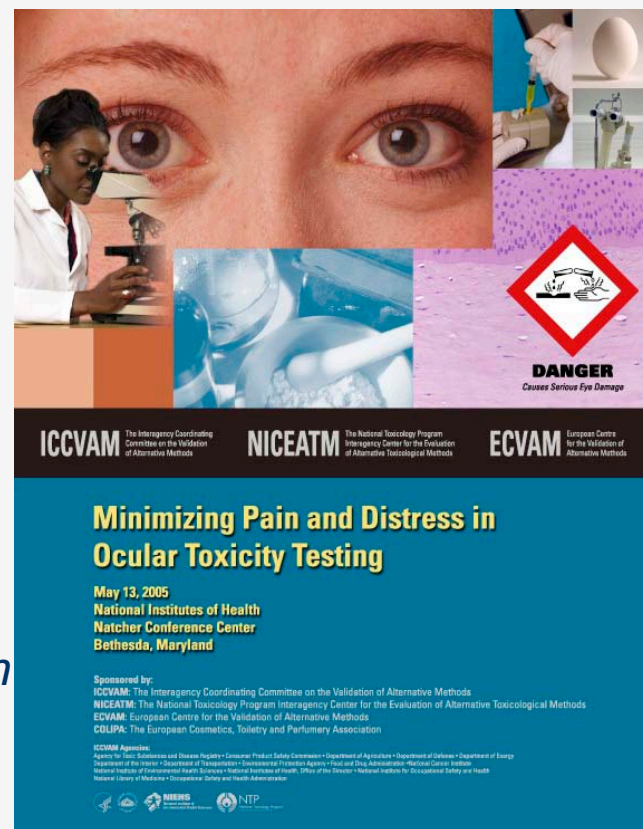


Current Guidance on Minimizing Pain and Distress in Ocular Safety Testing (2)

- U.S. Public Health Service Policy and U.S. Department of Agriculture regulations state that more than momentary or slight pain and distress
 - Must be limited to that which is unavoidable for the conduct of scientifically valuable research or testing
 - Must be conducted with appropriate pain relief medication unless justified in writing by the principal investigator
 - Continue for only the necessary amount of time
- Animals suffering severe or chronic pain or distress that cannot be relieved should be humanely killed after or, if appropriate, during the procedure

Workshop on Minimizing Pain and Distress in Ocular Toxicity Testing (2005)¹

- International symposium organized by ICCVAM, NICEATM, and ECVAM
- Evaluated the use of topical ophthalmic anesthetics and/or systemic analgesics during the conduct of the rabbit eye test
- Scientific experts at the workshop recommended:
 - *Routine pretreatment with topical anesthetics and systemic analgesics to prevent pain*
 - *Treatment with systemic analgesics of animals with ocular lesions associated with painful conditions and/or clinical signs of pain or distress*
 - *Adverse responses that could serve as earlier more humane endpoints to terminate animals on a study*



¹Available at: <http://iccvam.niehs.nih.gov/meetings/ocumeet/sympinfo.htm>

Effect of Topical Anesthetic Pretreatment on *In Vivo* Ocular Irritation Hazard Classification

- NICEATM evaluated the effect of pretreatment with tetracaine hydrochloride (0.5% w/v) on the ocular irritancy potential of 97 formulations (ICCVAM, 2007)
- Topical anesthetic pretreatment had little or no impact on:
 - The hazard classification severity category
 - The nature of the ocular irritation responses
 - The number of days for ocular lesions to clear

ICCVAM International Peer Review Panel Meeting: Ocular Safety Testing (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 *in vivo* low volume 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

ICCVAM Agencies:

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

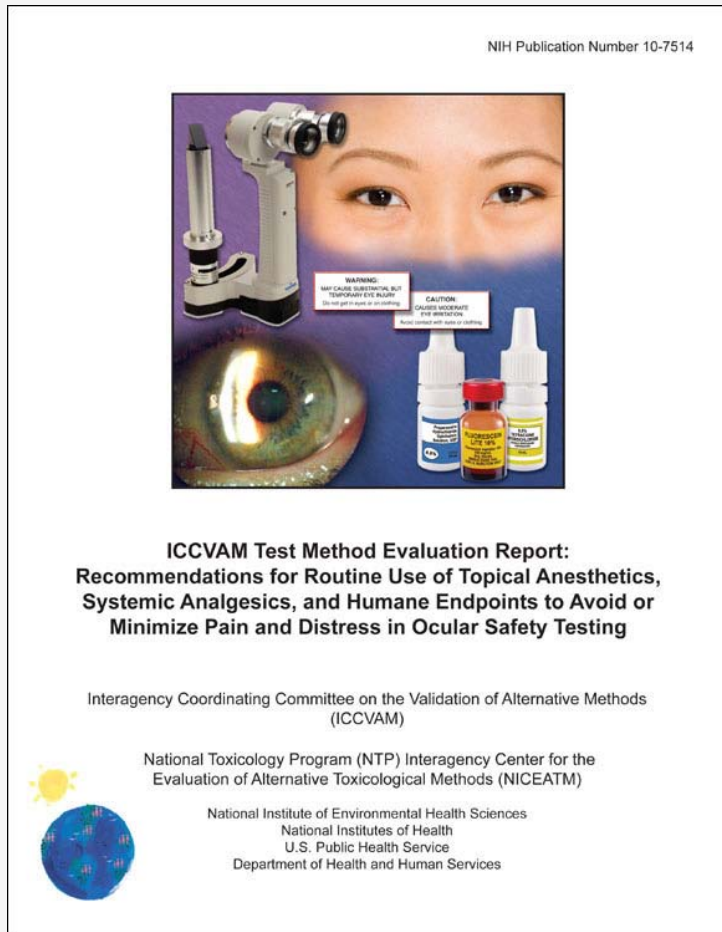


ICCVAM. 2009. Available:

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

- 22 scientists, 6 countries
- Evaluated 10 alternative methods and strategies, including
 - Routine use of systemic analgesics, topical anesthetics, and humane endpoints
- Panel report published July 2009
- Panel recommended:
 - An alternative preemptive pain management plan be applied to all *in vivo* rabbit eye tests intended for regulatory safety testing, unless there is a requirement for monitoring the pain response (e.g., pharmaceutical tolerability testing).

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



- ICCVAM test method evaluation report and recommendations published September 2010
- Federal agency responses due to ICCVAM March 7, 2011
 - Many available now
 - NIEHS
 - NIH
 - NIOSH
 - NLM
 - OSHA
 - DOD
 - Department of Interior

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

ICCVAM Recommendations: Routine Use of Topical Anesthetics and Systemic Analgesics

- ICCVAM recommends that balanced preemptive pain management should *a/ways* be provided when the rabbit eye test is conducted for regulatory safety testing
- Pain management should include:
 - Topical anesthetic and systemic analgesic prior to test substance administration (TSA)
 - Systemic analgesics after TSA (additional treatments as necessary)
 - Scheduled evaluations and recording of all clinical signs, especially those that may be indicative of pain and/or distress
 - Scheduled evaluations and recording of all eye injuries for nature, severity, and progression

ICCVAM-Recommended Pain Management Procedures: Pre-Test Substance Administration, Day 0

- **60 minutes before test substance administration:**
 - *Administer 0.01 mg/kg buprenorphine subcutaneously to provide a therapeutic level of systemic analgesia*

- **5 minutes before test substance administration:**
 - *Apply one or two drops of a topical ocular anesthetic to each eye*
 - 0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride
 - If the test substance is anticipated to cause significant pain and distress, consider applying more than one dose of topical anesthetic at five-minute intervals before test substance administration
 - Users should be aware that multiple applications of topical anesthetics could increase the severity and/or extend the time required for lesions that are chemically-induced to clear

ICCVAM-Recommended Pain Management Procedures: Post-Test Substance Administration, Day 0

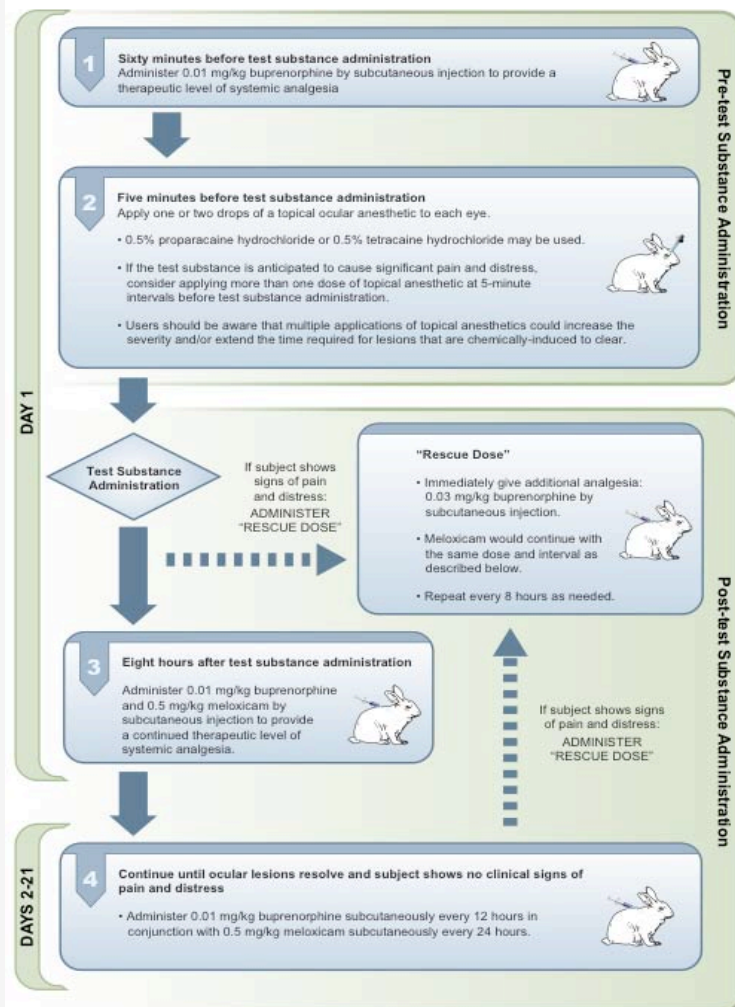
- **Post-test substance administration (TSA):**
Additional pain management via systemic analgesics only; no topical drugs
 - *If post-TSA, subject shows signs of pain and distress:*
Administer Rescue Dose
 - *0.03 mg/kg buprenorphine and 0.5 mg/kg meloxicam subcutaneously*
 - **Otherwise:**
 - **Eight hours after test substance administration:**
 - *0.01 mg/kg buprenorphine and 0.5 mg/kg meloxicam subcutaneously to provide a continued therapeutic level of systemic analgesia*

ICCVAM-Recommended Pain Management Procedures: Days 1-21

- ***Continue pain management with systemic analgesics until 1) ocular lesions resolve and 2) subject shows no clinical signs of pain and distress:***
 - *0.01 mg/kg buprenorphine subcutaneously every 12 hours*
 - *0.5 mg/kg meloxicam subcutaneously every 24 hours*



ICCVAM-Recommended Pain Management Procedures: Summary



Humane Endpoints

- Criteria that can be used as the basis for ending a test procedure early in order to avoid further pain and distress, OR
- Ideally, criteria that can be used to end a procedure *before* the onset of animal pain and distress

Stokes (2000). ILAR J. 41:59-61; Stokes (2002). ILAR J. 43:S31-38

ICCVAM Recommendations on the Routine Use of Humane Endpoints in Ocular Safety Testing (1)

- Several ocular lesions¹ can be used as earlier humane endpoints to terminate studies before the end of the scheduled 21-day observation period.
 - Endpoints currently accepted for study termination (OECD 2002)
 - Corneal opacity score of 4 that persists for 48 hours
 - Corneal opacity score of 4 is defined as: Opaque cornea, iris not discernable through the opacity
 - Corneal perforation or significant corneal ulceration including staphyloma
 - Blood in the anterior chamber of the eye
 - Absence of light reflex that persists for 72 hours
 - Absent light reflex corresponds to iris severity score of 2
 - Ulceration of the conjunctival membrane
 - Necrosis of the conjunctiva or nictitating membrane
 - Sloughing (separation of necrotic tissue from the living structure)

¹These lesions are considered predictive of severe irritant or corrosive injuries, and injuries that are not expected to fully reverse by the end of the 21-day observation period after treatment



ICCVAM Recommendations on the Routine Use of Humane Endpoints in Ocular Safety Testing (2)

- Severe depth of injury (e.g., corneal ulceration extending through the epithelium and into the superficial layers of the stroma)
- Destruction of more than 50% of the limbus, as evidenced by blanching of the conjunctival tissue
- Severe eye infection (purulent discharge)

ICCVAM Recommendations on the Routine Use of Humane Endpoints in Ocular Safety Testing (3)

- Several other ocular lesions can be used in combination for clinical decisions to terminate a study early:
 - Vascularization of the cornea surface (i.e., pannus)
 - Area of fluorescein staining not diminishing over time based on daily assessment
 - Lack of re-epithelialization 5 days after test substance application
- A qualified laboratory animal veterinarian should perform a clinical exam to determine if the combination of these effects warrants early study termination

ICCVAM Recommendations for Changes to Ocular Safety Testing Protocols (1)

- **One hour post TSA and then daily:** Comprehensive evaluations for the presence or absence of ocular lesions followed by at least daily evaluations
 - Animals should be evaluated at least once daily for the first 3 days to ensure that termination decisions are made in a timely manner
 - Continue analgesics as long as lesions are present
- **AT LEAST TWICE DAILY:** Test animals should be routinely evaluated for clinical signs of pain and/or distress (minimum of 6 hours between observations). Examples of relevant clinical signs include¹:
 - Repeated pawing or rubbing of the eye
 - Excessive blinking
 - Excessive tearing

¹Wright et al. (1985). Lab Anim. 19:20-36; NRC 2008, 2009

ICCVAM Recommendations on Changes to Ocular Safety Testing Protocols (2)

- A written record of all observations should be kept for determinations on the progression or resolution of ocular lesions
- A slit-lamp biomicroscope should be used when considered appropriate (e.g., assessing depth of injury when corneal ulceration is present)
- Digital photographs should be taken to document ocular lesions and to help assess their severity, progression, and resolution

Proposal to Update OECD TG 405: Acute Eye Irritation/Corrosion

- NICEATM-ICCVAM submitted an OECD Standard Project Submission Form (SPSF) in January 2010 proposing consideration for updates to TG 405
 - To incorporate the routine use of topical anesthetics, systemic analgesics, and humane endpoints in order to avoid or minimize pain and distress when the rabbit eye test is necessary to meet regulatory safety testing requirements
- OECD SPSF Consideration
 - March 2010: Rejected on grounds it would encourage more animal testing and less *in vitro* testing
 - October 2010: SPSF resubmitted, emphasizing that most OECD countries only allow animals to be used when *in vitro* test methods are not appropriate or do not provide sufficient information for hazard classification; Expedited consideration requested

Acknowledgements

- ICCVAM
- ICCVAM Interagency Ocular Toxicity Working Group
- ICCVAM Independent Scientific Peer Review Panel
- NICEATM Staff

Thank you for your attention.

Questions?

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<http://iccvam.niehs.nih.gov/>



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