

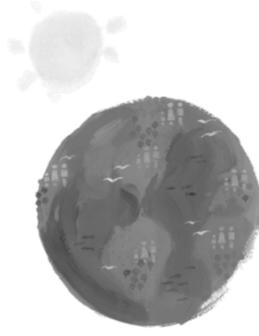
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*National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods*

*Interagency Coordinating Committee on
the Validation of Alternative Methods*

**Report on the Independent
Peer Review Panel:
Alternative Ocular Safety
Testing Methods**



Introduction and Overview

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ICCVAM-OTWG Co-Chair**

**June 25, 2009
SACATM Meeting
Arlington, VA**



**This presentation reflects the views of the author,
has not been reviewed or approved by, and may not
necessarily reflect the views of the U.S. Food and
Drug Administration.**



Ocular Safety Testing and Hazard Labeling: Public Health Importance

- Accidental eye injury is a leading cause of visual impairment in the U.S.¹
- Many injuries occur due to contact with workplace or household chemicals
- In the home, about 125,000 eye injuries per year are caused by accidents involving common household products; many of these are caused by chemical products³
 - Chemical burns to eyes resulting in emergency room visits often caused by products such as adhesives, automotive chemicals, household cleaners, and bleach⁴
- Over 100 American workers per day experience an eye injury resulting in time away from work; many of these are caused by chemicals or chemical products²

¹American Academy of Ophthalmology

²U.S. Bureau of Labor Statistics, 2007

³American Academy of Ophthalmology

⁴CPSC NIESS Database, 2007



Eye Injuries “On the Job” by Injury Source—2007¹

| Source | Number | Percent |
|---|---------------|--------------|
| Chemicals & chemical products | 5,260 | 15 |
| Containers | 890 | 3 |
| Furniture & fixtures | 280 | <1 |
| Machinery | 430 | 1 |
| Parts & materials | 2,570 | 8 |
| Floors, walkways or ground surfaces | 80 | <1 |
| Hand tools | 1,940 | 6 |
| Vehicles | 530 | 2 |
| Person (self or other) | 700 | 2 |
| Other sources & non-classifiable | 20,330 | 62 |
| All Eye Injuries | 33,010 | 100 |

¹Source: Bureau of Labor Statistics; injuries involving days away from work; private industry only



The Lash-Lure Tragedy (c. 1930)



- The Ad Read:
 - “The New and Improved Eye Brow and Eye Lash Dye **Lash Lure** Radiates Personality”
- The Actual Effects:
 - Allergic reactions
 - Severe pain
 - Blindness
 - Death

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Statutes and Regulations Requiring Ocular Corrosivity / Irritation Testing

| Agency | Authority | Regulation | Guideline |
|--------|---------------------------------|------------------------------------|--------------------|
| EPA | FIFRA (1947) TSCA (1977) | 40CFR | OPPTS 870.2400 |
| CPSC | FHSA (1964) | 16CFR1500 | 16CFR1500.42 |
| FDA | FDCA (1938) | 21CFR | 16CFR1500.42 |
| OSHA | OSHA (1970) | 29CFR | 16CFR1500.42 |
| EU | Council Directive 67/548/EEC | Commission Directive 2004/73/EC | Annex V B.5 |
| OECD | - | - | Test Guideline 405 |

CFR: Code of Federal Regulations; CPSC: Consumer Product Safety Commission; EPA: Environmental Protection Agency; EU: European Union; FDA: Food and Drug Administration FDCA: Food, Drug and Cosmetic Act; FHSA: Federal Hazardous Substances Act; FIFRA: Federal Insecticide, Fungicide, and Rodenticide Act; OECD: Organisation for Economic Co-operation and Development; OPPTS: EPA, Office of Prevention, Pesticides, and Toxic Substances; OSHA: Occupational Safety and Health Administration; TSCA: Toxic Substances Control Act

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Timeline for ICCVAM Evaluation

2009

- Mar 31 *Federal Register (FR)* Notice: announcement of independent scientific peer review panel meeting; availability of documents; request for public comments
- May 19-21 Ocular Peer Review Panel Meeting (public)
- Jun 25-26 SACATM Meeting: Panel conclusions and recommendations presented for comments**
- Jul 8 *FR* Notice: announcement of publication of Panel report; request for public comments
- Dec Transmittal of ICCVAM recommendations to Federal agencies

2010

- Jun Federal agency responses due to ICCVAM

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Alternative Ocular Safety Testing Methods and Approaches Evaluated by the Panel

1. Routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress during *in vivo* ocular irritation testing
2. Validation status of four *in vitro* test methods for identifying mild/moderate ocular irritants and substances not labeled as irritants
 - Bovine corneal opacity and permeability (BCOP)
 - Isolated chicken eye (ICE)
 - Hen's egg test – chorioallantoic membrane (HET-CAM)
 - Isolated rabbit eye (IRE)
3. Validation status of the *in vivo* low volume eye test (LVET)
4. Validation status of the individual test methods and testing strategies to assess eye irritation potential of antimicrobial cleaning products (AMCPs)
 - Cytosensor Microphysiometer® (CM)

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Routine Use of Topical Anesthetics: Current Guidelines and Scientific Workshops

- The U.S. Consumer Product Safety Commission (CPSC) has recommended the pre-application of tetracaine ophthalmic anesthetic for all rabbit eye toxicity studies (CPSC 1984).
- Current U.S. EPA and OECD test guidelines for the rabbit eye test state that topical anesthetics can only be used if the user demonstrates that such pretreatments do not interfere with the results of the tests (EPA 1998; OECD 1987).
 - For this reason, they are not often used because a separate study to provide such information would often be necessary.
- IRAG (1991) and NICEATM/ICCVAM/ECVAM (2005) scientific workshops
 - Participating experts agreed that:
 - Pretreatment with pre-emptive analgesia is more effective than waiting to treat after the onset of pain, and is commonly practiced in veterinary medicine
 - Combinations of general or topical anesthesia and systemic analgesia should be routinely used to avoid pain
 - Induced lesions should be treated with continued systemic analgesia during the observation period (e.g., buprenorphine)

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ICCVAM Draft Recommendations: Routine Use of Topical Anesthetics and Systemic Analgesics

- *ICCVAM proposes the routine use of a topical anesthetic (i.e., tetracaine or proparacaine, 1-2 drops of 0.5% w/v solution) and an opioid systemic analgesic (i.e., buprenorphine, 0.05 mg/kg) prior to instillation of a test substance, unless there is an adequate scientific rationale for not using these substances*
 - *Anti-inflammatory analgesics (e.g., nonsteroidal anti-inflammatory drugs) are not recommended because of their possible influence on study results due to demonstrated effects on the wound healing process.*
- *Treatment with an opioid systemic analgesic (i.e., buprenorphine, 0.05 mg/kg, q 12 hr) should continue as long as a test animal displays clinical signs of more than momentary or slight pain or distress (e.g., blepharospasm, excessive lacrimation, pawing at the treated eye) or has ocular injuries expected to cause or be associated with pain or distress (e.g., opacity, iritis, conjunctival redness, chemosis scores ≥ 2).*

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Use of Humane Endpoints: Current Guidelines and Scientific Workshops

- Public Health Service Policy and U.S. Department of Agriculture regulations on laboratory animals state that more than momentary or slight pain and distress:
 - Be limited to that which is unavoidable for the conduct of scientifically valuable research or testing
 - Be conducted with appropriate pain relief medication unless justified in writing by the principal investigator
 - Continue for only the necessary amount of time required to attain the scientific objectives of the study
- IRAG (1991) and NICEATM/ICCVAM/ECVAM (2005) scientific workshops
 - Participating experts agreed that ocular lesions (listed on next slide), considered to be predictive of a severe or corrosive irritant response and not expected to fully reverse within the 21-day post-treatment period, should be used as humane endpoints.

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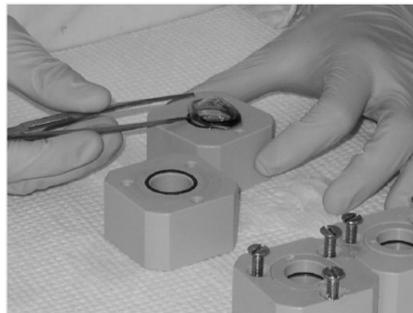
ICCVAM Draft Recommendations: Use of Humane Endpoints

- ICCVAM recommends the following ocular lesions be used as humane endpoints to terminate studies early, where deemed appropriate:
 - *Endpoints currently accepted for study termination (OECD 2000)*
 - *Vascularization of the corneal surface (i.e., pannus)*
 - *Greater than 75% of the limbus destroyed*
 - *Area of fluorescein staining not diminishing over time (daily assessment)*
 - *Lack of re-epithelialization five days after test substance application*
 - *Extent of depth of injury to the cornea (routinely using slit-lamp and fluorescein staining) where corneal ulceration extends beyond superficial layers of the stroma or the depth of injury increases over time*

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BCOP Test Method

1. Fresh bovine eyes are collected from abattoir.
2. Corneas are dissected and equilibrated.
3. Test substances are applied to the corneas.
 - Liquids are tested at 100% for 10 min at 32°C followed by a second incubation with medium for 2h at 32°C.
 - Solids are tested at 20% for 4h at 32°C.
4. Final opacity measurements are taken.
5. Fluorescein is added and the corneas are incubated.
6. Fluorescein readings (OD_{490}) are taken.
7. *In Vitro* Score = opacity value + 15 x OD_{490} value
8. Corneas are fixed, if histology is performed.



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BCOP Test Method Data

- The database from the assessment of the BCOP test method for its ability to identify ocular corrosive/severe irritants (ICCVAM 2006) has been supplemented with results from 66 AMCPs.
 - A total of 211 substances.
- Sufficient *in vivo* data were available for a subset of these substances to assign an ocular irritancy classification according to the EPA, EU, and GHS classification systems.
 - EPA : 187 substances
 - EU: 118 substances
 - GHS: 187 substances

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ICCVAM Draft Recommendations for BCOP: Usefulness and Limitations (1)

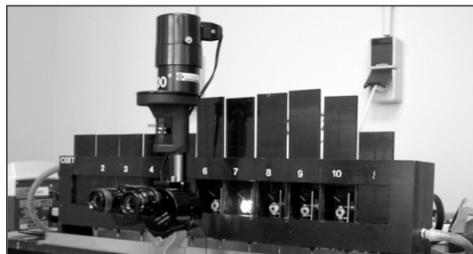
- The BCOP test method has been previously recommended for identification of **ocular corrosives and severe irritants** (i.e., EPA Category I, EU R41, and GHS Category 1) in appropriate circumstances and with certain limitations.
- ICCVAM proposes that the BCOP test method is not recommended to identify substances from **all** hazard categories as defined by the GHS, EPA, and EU classification systems (EPA 1996; EU 2001; UN 2003).
 - Overall correct classifications ranged from 49% (91/187) to 54% (101/186), depending on the hazard classification system evaluated when using the entire database.
 - Overall correct classifications ranged from 47% (31/66) to 54% (35/65) depending on the hazard classification system evaluated when discordant classes are removed.

ICCVAM Draft Recommendations for BCOP: Usefulness and Limitations (2)

- The BCOP test method can be used as a screening test to identify **substances not labeled as irritants** (i.e., EU Not Labeled, GHS Not Classified), from all other hazard categories (i.e., EU R41 or R36; GHS Category 1, 2A, or 2B) when results are to be used only for EU or GHS hazard classifications.
 - Overall accuracy ranged from 64% (76/118) to 83% (154/186) depending on the hazard classification system used.
 - False positive rates ranged from 53% (24/45) to 70% (63/90) depending on the hazard classification system used.
 - False negative rates were 6% (8/141) for the EPA system and 0% (0/54 or 0/97) for the EU and GHS systems, respectively.
 - Among the eight false negatives for the EPA system, 100% (8/8) were EPA Category III substances based on Draize data.
 - Due to the severity of lesions (i.e., conjunctival redness not cleared until Day 7) associated with 50% (4/8) of the EPA Category III substances that were false negative in the BCOP test method the BCOP test method cannot be recommended as a screening test to identify EPA Category IV substances.

ICE Test Method

1. Fresh chicken heads are obtained from abattoir.
2. Eyes are dissected out, mounted in apparatus and equilibrated.
3. Test substances are applied to the corneas as a single dose.
 - 30 μ L for liquids for 10 sec
 - 30 mg for solids for 10 sec
4. Corneal reactions are measured at regular intervals up to 4 hours post-treatment and mean values for each parameter (corneal swelling, corneal opacity, and fluorescein retention) are determined.
5. Based on the maximum mean values¹ of these measurements, the irritation potential of the test substance is defined.



¹For each endpoint, the mean of three eyes is recorded for each time point and the largest mean value is used for scoring.

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ICE Test Method Data

- The database was unchanged from the assessment of the ICE test method (ICCVAM 2006) for its ability to identify ocular corrosive/severe irritants.
 - A total of 174 substances.
- Sufficient *in vivo* data were available for a subset of these substances to assign an ocular irritancy classification according to the EPA, EU, and GHS classification systems
 - EPA : 140 substances
 - EU: 153 substances
 - GHS: 141 substances

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ICCVAM Draft Recommendations for ICE : Usefulness and Limitations (1)

- *The ICE test method has been previously recommended for identification of **ocular corrosives and severe irritants** (i.e., EPA Category I, EU R41, GHS Category 1) in appropriate circumstances and with certain limitations.*
- ICCVAM proposes that the ICE test method not be recommended to identify **all** categories of ocular hazard classification as defined by the EPA, EU, and GHS classification systems (EPA 1996; EU 2001; UN 2003).
 - *The overall correct classifications ranged from 59% (83/141) to 77% (118/153), depending on the hazard classification system evaluated when using the entire database.*
 - *The overall correct classifications ranged from 64% (49/77) to 80% (66/82) depending on the hazard classification system evaluated when discordant classes are removed.*

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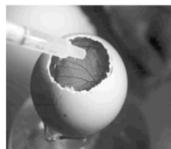
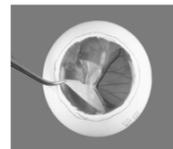
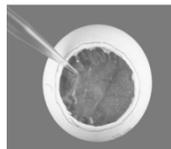
ICCVAM Draft Recommendations for ICE: Usefulness and Limitations (2)

- *The ICE test method is not recommended as a screening test to identify **substances not labeled as irritants** (i.e., EPA Category IV, EU Not Labeled, GHS Not Classified) from all other hazard categories (i.e., EPA Category I, II, or III; EU R41 or R36; GHS Category 1, 2A, or 2B) as defined by the GHS, EPA, and EU classification systems (EPA 1996; EU 2001; UN 2003).*
 - *Overall accuracy ranged from 78% (110/141) to 85% (130/153) depending on the hazard classification system used.*
 - *False positive and false negative rates ranged from approximately 11% (10/93) to 34% (27/79) and 6% (4/62) to 22% (13/60), respectively whether or not discordant classes were included in the evaluation.*
 - *Among the false negatives, at least one substance was classified as an ocular corrosive/severe irritant based on Draize data (n = 1 each for the EPA and GHS systems, and n = 6 for the EU system).*

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HET-CAM Test Method

1. Fertilized eggs are incubated under optimized conditions for 9 days.
2. On day 10, eggs are opened and the CAM is exposed.
3. Test substances are applied to the CAM.
 - 300 μ L for liquids for 20 sec
4. The CAM is evaluated for development of irritant endpoints (hyperemia, hemorrhage, and coagulation) at 0.5, 2, and 5 min after rinsing off the test substance.
5. Irritant endpoints are subjectively assessed and a score is assigned based on the time required for development of each endpoint. The scores are totaled to yield a total irritation score for the test substance (maximum score of 21).



HET-CAM IS(A) Test Method Data

- The database was unchanged from the assessment of the HET-CAM test method (ICCVAM 2006) for its ability to identify ocular corrosive/severe irritants.
 - A total of 63 substances.
- Sufficient *in vivo* data were available for a subset of these substances to assign an ocular irritancy classification according to the EPA, EU, and GHS classification systems:
 - EPA : 60 substances
 - EU: 58 substances
 - GHS: 59 substances

ICCVAM Draft Recommendations for HET-CAM: Usefulness and Limitations (1)

- *The validation database has remained unchanged since the prior ICCVAM evaluation in 2006 and therefore the original recommendation remains unchanged.*
 - *The use of these analyses methods and decision criteria for screening and identifying **ocular corrosives and severe irritants** (i.e., EPA Category I, GHS Category 1, EU R41) in a tiered-testing strategy, as part of a weight-of-evidence approach, is not recommended.*
- ICCVAM proposes that the HET-CAM test method is not recommended to identify substances from **all** hazard categories as defined by the GHS, EPA, and EU classification systems (EPA 1996; EU 2001; UN 2003).
 - *Overall correct classifications ranged from 40% (23/58) to 41% (24/59), depending on the hazard classification system evaluated.*

ICCVAM Draft Recommendations for HET-CAM: Usefulness and Limitations (2)

- The HET-CAM IS(A) test method can be used as a screening test to identify **substances not labeled as irritants** (i.e., EU Not Labeled, GHS Not Classified), from all other hazard categories (i.e., EU R41 or R36; GHS Category 1, 2A, or 2B) when results are to be used only for EU or GHS hazard classifications.
 - *Overall accuracy ranged from 58% (36/58) to 60% (47/60) depending on the hazard classification system used.*
 - *False positive and false negative rates ranged from approximately 60% (9/15) to 69% (22/32) and 0% (0/26) to 9% (4/45), respectively.*
 - *Limited database indicates that HET-CAM could identify substances labeled as EPA Category IV.*
 - *However, the database does not include substances that are actually regulated by EPA (e.g., pesticide formulations).*
 - *For this reason, additional testing of such products in HET-CAM may be necessary before definitive recommendations can be made on its usefulness for identifying EPA Category IV substances.*

IRE Test Method

1. Eyes are obtained from rabbits euthanized for other purposes.
2. Test substances are applied over the corneas.
 - Liquids are applied using a syringe.
 - Solids are pulverized and applied as a powder.
3. The effects of the test substance are measured quantitatively as an increase in thickness (swelling), subjectively as scores for corneal opacity, the area of corneal involvement, and fluorescein penetration, and descriptively as morphological changes to the corneal epithelium.
4. The number of ocular parameters and the number of time points measured varies from study to study.



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IRE Test Method Data

- Data from four published studies were examined for decision criteria that would facilitate the classification of moderate/mild irritants.
- The different endpoints (and time points) measured has impeded the classification of substances as severe, moderate, mild, or not labeled as irritants.
- Lack of a standardized protocol has made substance classification difficult.

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ICCVAM Draft Recommendations for IRE: Usefulness and Limitations

- *The lack of a widely accepted, standardized IRE test method for detecting ocular irritants has confounded efforts to evaluate the IRE test method for its usefulness as a partial or full replacement for the Draize rabbit eye test.*
- *The validation database has remained unchanged since the prior ICCVAM evaluation in 2006 and therefore the original recommendation remains unchanged.*
 - *The use of the IRE test method for screening and identifying **ocular corrosives and severe irritants** [i.e., EPA Category I, GHS Category 1, EU R41] in a tiered-testing strategy, as part of a weight-of-evidence approach, is not recommended.*
 - *There also are insufficient data using all four recommended IRE endpoints (corneal opacity, fluorescein penetration, corneal swelling, and observations of significant effect on corneal epithelium) to assess test method accuracy and reliability when all these endpoints are evaluated in a single study.*

Comparison of LVET and Draize Protocols

| | LVET | Draize |
|----------------------------------|----------------------------------|---|
| Dose Volume | 10 µL | 100 µL |
| Dose Location | Applied directly onto the cornea | Applied into the lower conjunctival sac |
| Eyelid Closure | No forced eyelid closure | Eyelids held closed for 1 second |
| Scale for Scoring Ocular Lesions | Draize | Draize |

LVET Advantages and Limitations

- Reported advantage
 - LVET is less overpredictive of the human response
- Identified limitations
 - Underpredicts severe irritants compared to Draize¹
 - When using the EPA hazard classification system, 70% (7/10) of Draize Category I substances were underpredicted as Category II (n=1) and Category III (n=6) in the LVET.
 - When using the GHS hazard classification system, 100% (8/8) of Draize Category 1 substances were underpredicted as Category 2B (n=4) and Not Labeled (n=4) in the LVET.
 - Limited data to evaluate the extent of underprediction relative to known human severe ocular irritants.
 - Human accidental exposure data
 - Three substances, which were “recognized as slightly irritating, moderately irritating, or severely irritating/corrosive to humans” (Griffith et al. 1980) had corresponding LVET and Draize summary data that indicated these substances were not reversible within 21 days (i.e., EPA Category I).
 - Human clinical study data limited to mild/minimally irritating substances

¹Data from CTFA Phase III Study, which consisted of 25 surfactant-based formulations (Gettings et al. 1996).

LVET Method Data

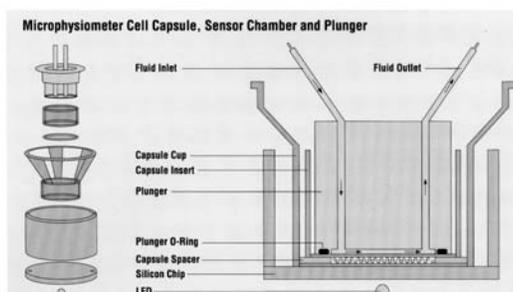
- Data derived from 10 published studies were considered.
- The International Association for Soaps, Detergents and Maintenance Products (A.I.S.E.) submitted a background review document (BRD) in February 2007 to the European Centre for the Validation of Alternative Methods (ECVAM) for an independent peer review by their Scientific Advisory Committee (ESAC).
 - ECVAM has agreed to make this BRD publicly available for review and comment.
 - Based on a May 2009 communication, industry indicated they will not allow release of the BRD until after the ESAC peer review is completed.

ICCVAM Draft Recommendations for LVET: Usefulness and Limitations

- A review of available data regarding the usefulness and limitations of the LVET determined that:
 - LVET under-predicts severe irritants compared to the Draize
 - The LVET data, and comparative Draize rabbit data with which to evaluate the accuracy of the LVET, are available for limited types and numbers of substances (e.g., predominantly surfactant-containing personal and household cleaning products)
 - There are insufficient data to evaluate the extent of under-prediction relative to known human severe ocular irritants
- ICCVAM proposes that the LVET has not been adequately validated and does not have adequate demonstrated performance (sensitivity and specificity) to serve as an acceptable reference test method against which to determine the validity of in vitro alternative test methods for hazard classification and labeling purposes.

Cytosensor Microphysiometer (CM) Test Method

1. Cells (mouse L929 fibroblasts) are grown on a Transwell membrane.
2. Cells are exposed to medium containing the test material for a specified duration of time.
3. Cells are rinsed.
4. The pH change (detection of acidity) is measured.
5. The concentration of test material needed to reduce the acidification rate by 50% is the MRD₅₀.



Cytosensor Microphysiometer (CM) Test Method Data

- Database of 53 water-soluble surfactants
 - 32 surfactant-containing formulations
 - Most are limited to cosmetic and personal care products, contain one or more surfactants at a final concentration of greater than 5%.
 - No pesticide formulations included in this validation database.
 - 21 surfactant chemicals
- Database of 29 water-soluble nonsurfactants
 - 27 nonsurfactant chemicals
 - 2 nonsurfactant formulations



ICCVAM Draft Recommendations for CM: Usefulness and Limitations (1)

- *ICCVAM proposes that the Cytosensor test method can be used as a screening test to identify water-soluble substances as **ocular corrosives and severe irritants** (i.e., EPA Category I, GHS Category 1, EU R41) in a tiered-testing strategy, as part of a weight-of-evidence approach.*
 - *Surfactant-containing substances: 9-22% (2/23-5/23) false negatives; 3-10% (1/30-3/29) false positives*
 - *Nonsurfactant substances: 43-55% (3/7-6/11) false negatives; 0-6% (0/18-1/18) false positives*
- *A substance that tests negative with Cytosensor would need to be tested in another test method that is capable of identifying possible in vitro false negative severe irritants and ocular corrosives and to distinguish between moderate and mild ocular irritants.*



ICCVAM Draft Recommendations for CM: Usefulness and Limitations (2)

- ICCVAM proposes that the Cytosensor test method can be used as a screening test to identify water-soluble surfactant chemicals and certain types of surfactant-containing formulations (e.g., cosmetics and personal care product formulations, but not pesticide formulations) as **substances not labeled as irritants** (i.e., EPA Category IV, GHS Category NL, EU Category NL) in a tiered-testing strategy, as part of a weight-of-evidence approach.
 - Surfactant-containing substances: 0-2% (0/27-1/46) false negatives; 50-69% (3/6-18/26) false positives
- However, based on the false positive rate, a substance that tests positive with the Cytosensor test method would need to be tested in another test method that is capable of correctly identifying possible *in vitro* false positives
- Due to the high false negative rate for Cytosensor when testing water-soluble nonsurfactant substances and formulations, Cytosensor is not recommended as a screening test to identify **substances not labeled as irritants** among these types of substances.
 - Nonsurfactant substances: 24-38% (5/21-8/21) false negatives; 25-40% (1/4-2/5) false positives

Distribution of EPA Categories for Ocular Irritants for Registered Antimicrobial Chemicals¹

| EPA Category | Number of Studies | Total (%) |
|------------------|-------------------|-----------|
| I ² | 73 | 64 |
| II ³ | 13 | 11 |
| III ⁴ | 16 | 14 |
| IV ⁵ | 13 | 11 |
| Total | 115 | 100 |

¹Database from Dec 19, 2007 - Jan 15, 2009.

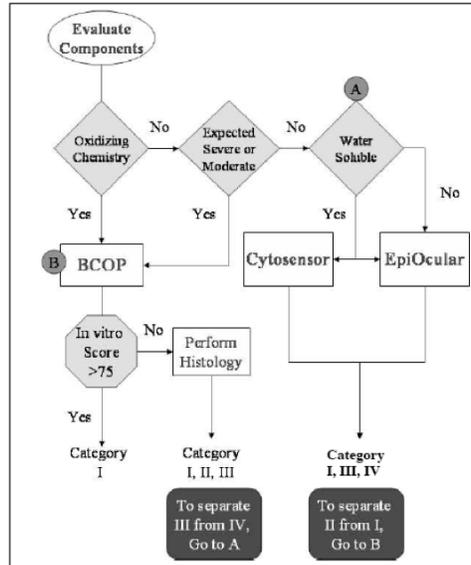
²Category I: Supported by studies or cited as similar (n=43); waived (commonly due to pH corrosivity) (n=30)

³Category II: Supported by studies or cited as similar (n=13)

⁴Category III: Supported by studies or cited as similar (n=16)

⁵Category IV: Supported by studies or cited as similar (n=12); waived (n=1)

Original Testing Strategy Proposed in the AMCP BRD Submission



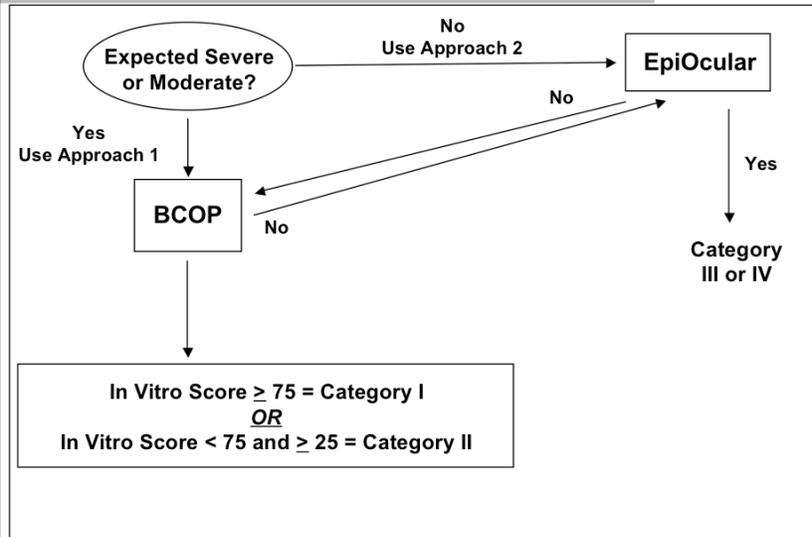
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Original Testing Strategy Proposed in the AMCP BRD Submission: Test Method Data

- None of the 228 substances included in the AMCP BRD were tested in all three *in vitro* test methods proposed for the testing strategy.
 - According to the submitter, “a minimum 28 of the materials are EPA registered anti-microbial cleaning products, with eight additional materials being in-use dilutions of concentrates which are EPA registered.”
- Therefore, there are no data available for the proposed substances with which to characterize the actual performance of a testing strategy that includes the BCOP, the CM, and the EO.

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Proposed Alternate Testing Strategy



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Proposed Alternate Testing Strategy: Test Method Data

- 28 substances were tested in both the BCOP and the EO for which Draize reference data were available.
 - One EPA Category II
 - Four EPA Category III

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Performance of AMCP Substances Tested in Both BCOP and EO

- Data were evaluated based on two approaches:
 - Approach 1: Test in BCOP first and then in EO
 - All Category I and II results would be classified.
 - All other substances would subsequently be tested in EO and classified as either Category III or IV.
 - Approach 2: Test in EO first and then in BCOP
 - All Category III and IV results would be classified.
 - All other substances would subsequently be tested in BCOP and classified as either Category I or II.
- Regardless of which approach was used, the overall performance of the proposed BCOP/EO testing strategy was the same.
 - None of the irritant categories (i.e., Category I, II, or III) were underclassified as Category IV substances.

ICCVAM Draft Recommendations for AMCP Testing Strategies: Usefulness and Limitations (1)

- *Given the limitations of the available database for three in vitro test methods (CM, EO, and BCOP), there are currently insufficient data with which to adequately demonstrate that an in vitro testing strategy using the BCOP, CM, and EO can identify all four required EPA hazard categories for ocular irritation/corrosion.*
 - None of the 228 AMCP included in the validation database have been tested in all three *in vitro* methods.

ICCVAM Draft Recommendations for AMCP Testing Strategies: Usefulness and Limitations (2)

- *Although the performance of a testing strategy using BCOP and EO appears to be useful for identifying Category I substances using BCOP and Category IV substances using EO, there are insufficient data with which to adequately demonstrate that this strategy can identify all four required EPA hazard categories for ocular irritation/corrosion.*
 - There are a limited number of AMCP (n = 28) that have been tested in both BCOP and EO.
 - Of these, there is only one EPA Category II substance and only four EPA Category III substances (based on Draize eye test results).
 - Regardless of which approach was used, the overall performance (79% [22/28]) of the proposed BCOP/EO testing strategy was the same.
- *Therefore, definitive recommendations on the usefulness and limitations of an in vitro testing strategy cannot be made at this time.*

ICCVAM Peer Panel Review Meeting



- May 19-21, 2009
 - CPSC Headquarters
 - Bethesda, MD
- Expert Scientific Panel
 - 22 scientists
 - 6 countries
- Purpose: Evaluation of the Validation Status of Alternative Ocular Safety Testing Methods and Strategies

ICCVAM Charges to the Peer Panel

- Review the ICCVAM draft BRDs for completeness and identify any errors or omissions (other relevant publications or available data, etc.)
- Evaluate the information in the draft BRDs and determine the extent to which each of the applicable ICCVAM criteria for validation and acceptance have been appropriately addressed
- Consider the ICCVAM draft test method recommendations for the following and comment on the extent to which they are supported by the information provided in the BRDs:
 - Proposed test method usefulness and limitations
 - Proposed recommended standardized protocols
 - Proposed test method performance standards
 - Proposed future studies

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