

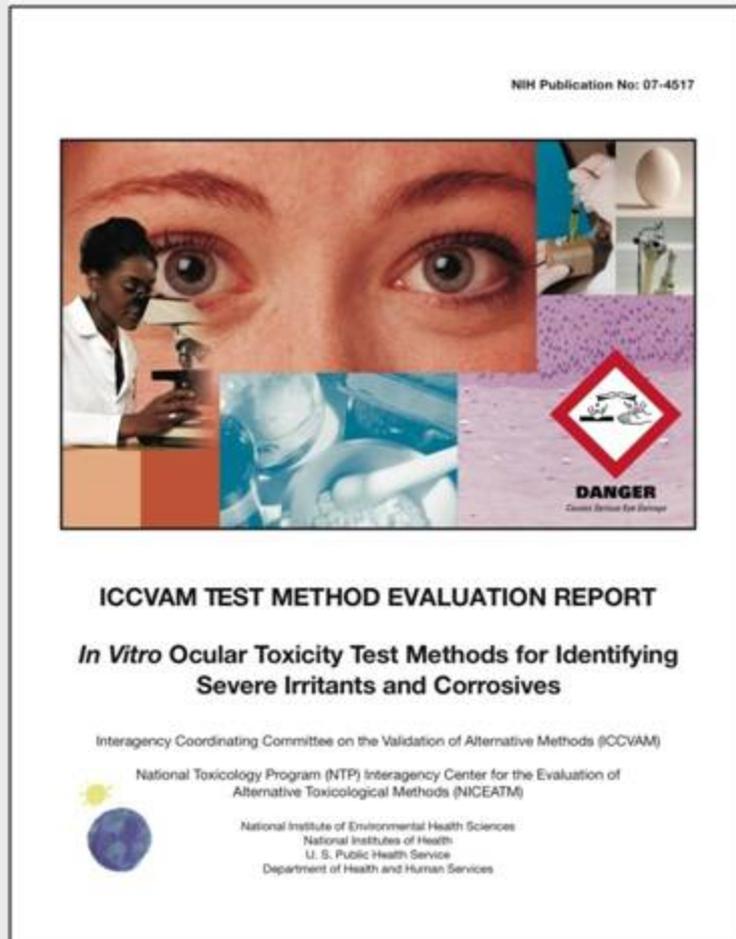
Availability and Regulatory Acceptance of ICCVAM- Recommended Alternative Test Methods



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

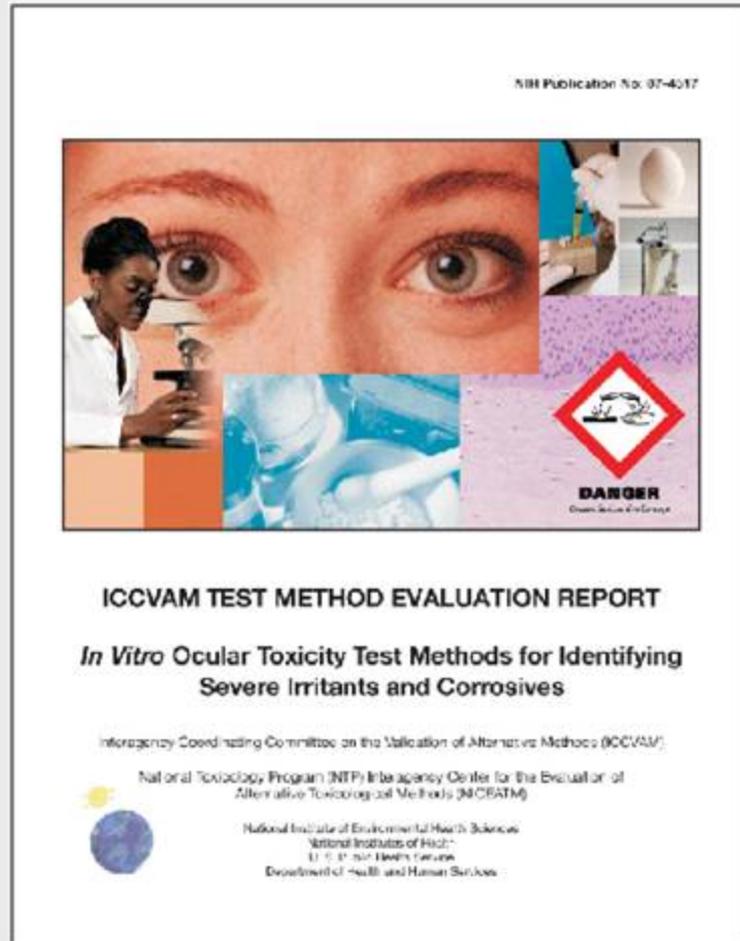
Ocular Toxicity: Agency Acceptance of ICCVAM Recommendations



- *In Vitro* Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives
 - U.S. acceptance, April, 2008
 - agencies concurred with ICCVAM recommendations and stated limitations, where applicable to their agency
 - International test guidelines adopted, June, 2009
 - These are the first validated *in vitro* alternative test methods adopted for worldwide regulatory use
 - Will likely reduce animal use for eye safety testing by 10 percent or more



ICCVAM Recommendations on Four Ocular Safety Testing Methods Accepted by US Agencies



- Bovine Corneal Opacity and Permeability (BCOP) assay
- Isolated Chicken Eye (ICE) assay
- Isolated Rabbit Eye (IRE) assay
- Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) assay



International Regulatory Acceptance: *In Vitro* Ocular Safety Testing Methods

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

DRAFT PROPOSAL FOR A NEW GUIDELINE 437

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

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

DRAFT PROPOSAL FOR A NEW GUIDELINE 438

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

- OECD Test Guidelines Submissions
 - ICCVAM and NICEATM developed drafts for BCOP and ICE in coordination with ECVAM and JaCVAM
 - Supported by ICCVAM Test Method Evaluation Report, Background Review Documents, Peer Review Panel Reports
- Timeline to OECD Adoption
 - Submitted in August, 2008
 - OECD Expert Consultation Meeting at EPA, Washington D.C., December 4-5, 2008
 - Approved at National Coordinators Meeting, March 31-April 2, 2009
 - **OECD Formal Adoption by Joint Meeting, June, 2009**
 - **TG 437:BCOP**
 - **TG 438:ICE**



ICCVAM Recommendations:

In Vitro Ocular Safety Testing Methods

- The BCOP and ICE test methods should be used in a tiered-testing strategy, where positive substances can be classified as ocular corrosives or severe irritants *without the need for animal testing*
 - Provides for Reduction and Refinement
- **These alternative methods should always be considered before using rabbits for ocular safety testing, and used where determined appropriate**
 - In accordance with USDA Animal Welfare Act regulations and Public Health Service Policy on Humane Care and Use of Laboratory Animals
- Animal Welfare Act responsibilities
 - *Principal Investigators:*
 - *Must provide narrative discussion of alternatives consideration in animal study protocols*
 - *Institutional Animal Care and Use Committees:*
 - *Must review the consideration of alternatives, and approve animal use*

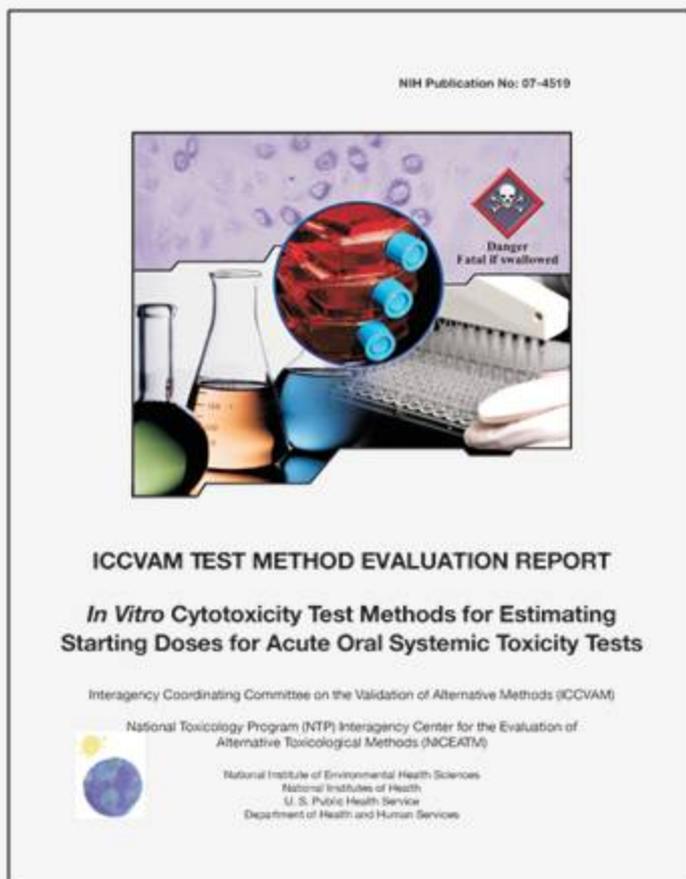


In Vitro Ocular Safety Testing Methods: ICCVAM Recommendations for Improvements

- **Expand the Validation Database**
 - Users encouraged to submit BCOP, ICE, and any *in vivo* data to NICEATM
 - Data will be used to reassess usefulness, limitations, and applicability domain for each test method
 - Post-marketing adverse event surveillance and human experience data also useful
- **Generate Histopathology Database**
 - Users encouraged to collect and process tissues for histopathology; forward results to NICEATM for further evaluation
 - Histopathology requested for BCOP, ICE, and rabbit tissues
 - Goal is to establish and validate histopathology decision criteria that can be used to improve the accuracy of BCOP and ICE
 - Protocols and Test Guidelines will then be updated to include histopathology



ICCVAM Recommendations: *In Vitro* Methods for Acute Systemic Toxicity



- *In Vitro* Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests
 - Agency Responses, August, 2008
 - **All agencies endorsed the ICCVAM recommendations with the stated limitations and where applicable to their agency**
 - Use of these methods does not require regulatory acceptance, as data will not be used for regulatory decisions
 - Forwarded to agencies for possible inclusion in test guidelines, and to increase awareness of their availability



ICCVAM Recommendations: *In Vitro* Methods for Acute Systemic Toxicity

- May be used in a weight-of-evidence approach to determine starting doses for current acute oral toxicity protocols
- **Should *always* be considered *before* using animals for acute oral toxicity testing, and should be used where determined appropriate**
- Where applicable, Principal Investigators should consider these alternatives, and IACUCs should review this consideration and approve animal use, in accordance with:
 - U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals
 - U.S. Government Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training



In Vitro Methods for Acute Systemic Toxicity: Impact on Animal Welfare

Reduction

- For some types of substances, weight-of-evidence approach will reduce the number of animals needed
 - Up to 50 percent reduction in animal use for “non-toxic” unclassified substances, compared to starting with default dose
 - 3 vs. 6 animals
 - Estimated that over 50% of all substances tested are unclassified for acute oral toxicity hazard

Refinement

- In some testing situations, the approach may also reduce the numbers of animals that die or need to be humanely killed
 - Applicable to more toxic substances ($LD_{50} < 175\text{mg/kg}$)



ICCVAM Recommendations: *In Vitro* Methods for Acute Systemic Toxicity

Limitations

- Currently not sufficiently accurate to predict acute oral toxicity for the purpose of regulatory hazard classification categories
- Will likely overestimate starting doses for substances with certain toxic mechanisms not expected to be active in 3T3 or NHK cells (e.g., those that are neurotoxic or cardiotoxic)
 - Therefore may not be appropriate for estimating starting doses for such substances



In Vitro Methods for Acute Systemic Toxicity: ICCVAM Recommendations for Improvements

- **Expand the *in vitro* database**
 - Additional comparative *in vitro* basal cytotoxicity data should be collected when rat acute oral toxicity testing is conducted
 - However, *in vivo* testing should not be conducted solely to collect this data
 - Both *in vitro* and *in vivo* data should be submitted to NICEATM for further analysis of the validity of these methods

- **Evaluate the *in vitro* database**
 - To further characterize the usefulness and limitations of these test methods
 - Advance the use of *in vitro* methods for assessing acute oral toxicity for regulatory hazard classification purposes



In Vitro Methods for Acute Systemic Toxicity: International Acceptance

- Draft OECD Guidance Document developed by NICEATM-ICCVAM
- Endorsed by ICCVAM, June 25, 2009
- To be forwarded to OECD for consideration and adoption, June 2009



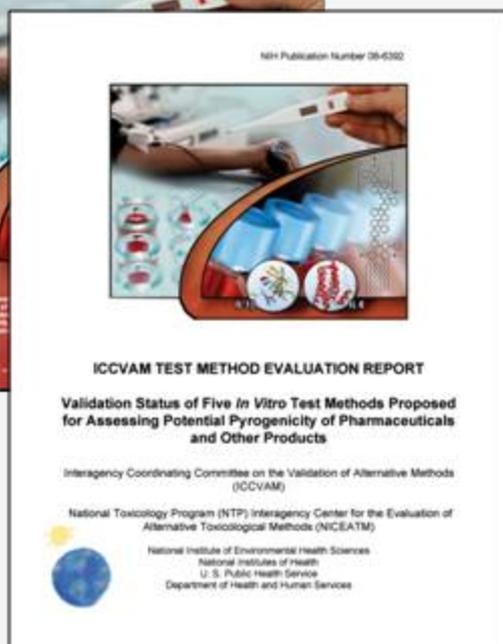
ICCVAM Recommendations: *In Vitro* Pyrogen Test Methods

Independent Scientific Peer Review: Five *In Vitro* Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products

February 6, 2007 | Natcher Conference Center | NIH Campus
8:30 a.m. - 5:00 p.m. | Conference Rooms E1/E2 | Bethesda, MD

ICCVAM
Interagency Coordinating Committee
on the Validation of Alternative Methods

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



- *ICCVAM Test Method Evaluation Report: Evaluation of Five In Vitro Pyrogen Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products*
- Agency responses received, April 2009
- **All Agencies endorsed the recommendations or indicated that they did not have relevant regulatory requirements**



ICCVAM Recommendations: *In Vitro* Pyrogen Test Methods

- Can be considered for use to detect Gram-negative endotoxin in human parenteral drugs on a case by-case basis, subject to product-specific validation to demonstrate equivalence to accepted pyrogen tests
- Should always be considered *before* using animals for pyrogen testing, and should be used where determined appropriate
- Recommendations provided for further research, development, and validation activities
 - To improve usefulness and broaden scope of use
 - To confirm extent that these methods can identify other pyrogenic substances in addition to Gram-negative endotoxin
- International Acceptance
 - European Pharmacopeia, March 2009



Questions for SACATM

How can we:

1. Increase awareness of these methods?
2. Encourage their consideration and use?
3. Encourage data submission and optional activities (e.g. histopathology) to aid in increasing usefulness of these methods?

