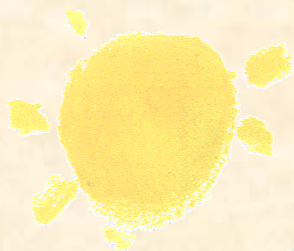


NICEATM

National Toxicology Program Interagency
Center for the Evaluation Of Alternative
Toxicological Methods

ICCVAM

Interagency Coordinating Committee
on the Validation of Alternative
Methods



Update on ICCVAM and NICEATM

William S. Stokes, D.V.M., D.A.C.L.A.M.
Director

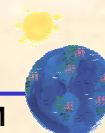
**NTP Interagency Center for the Evaluation
of Alternative Toxicological Methods**

**3rd Meeting of the Scientific Advisory
Committee on Alternative Toxicological
Methods**

**March 10-11, 2004
Bethesda, Maryland**

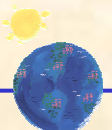


ICCVAM
NICEATM



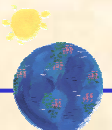
Outline

- **Agency responses to ICCVAM test recommendations**
- **Revised ICCVAM nomination and submission guidelines**
- **Agency representatives survey**
- **ECVAM collaborations**
- **Other activities**
- **ICCVAM Biennial Progress Report**



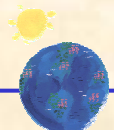
Additional ICCVAM and NICEATM Updates

- ICCVAM strategic planning initiative--*L. Schechtman and M. Wind*
- USDA report on animal use--*J. Kulpa-Eddy*
- Performance standards for *in vitro* dermal corrosivity test methods--*A. Rispin*
- *In vitro* test method nominations--*W. Stokes*
 - Estrogen receptor assays
 - Ocular irritation assays
- Vaccine potency tests--*J. Kulpa-Eddy*
- Evaluation of underprediction rate of the *in vivo* dermal corrosivity test --*W. Stokes and J. Haseman*



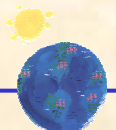
Agency Responses to ICCVAM Test Recommendations

- **Public Law 106-545:**
 - **ICCVAM submits test recommendations through the Secretary, DHHS, to appropriate Federal agencies**
 - **Agencies to respond within 180 days**
 - **ICCVAM makes available to the public**
 - **ICCVAM recommendations**
 - **Agency responses**



ICCVAM Acute Toxicity Test Recommendations

- Forwarded to agencies in March, 2003
- All 15 agencies responded
 - Posted on NICEATM-ICCVAM website
 - <http://iccvam.niehs.nih.gov>
- *Federal Register* notices announced availability of recommendations and responses



The Revised Up-and-Down Procedure for Acute Toxicity

NIH Publication No: 02-4501

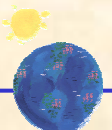


The Revised Up-and-Down Procedure: A Test Method for Determining the Acute Oral Toxicity of Chemicals Volume 1 of 2

Results of an Independent Peer Review Evaluation Organized by the Interagency
Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative
Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

- **ICCVAM recommendations:**
 - Valid replacement for LD50 for hazard classification
 - Reduces animal use (60-70%)
- **ICCVAM-ILSI-EPA Implementation Workshop - 2002**
- **Current regulatory acceptance**
 - EPA
 - CPSC
 - DOT
 - OECD (TG 425)
 - UN Transport
- **<http://iccvam.niehs.nih.gov>**



***In Vitro* Methods for Assessing Acute Systemic Toxicity**

NIH Publication No: 01-4499



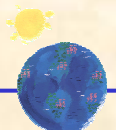
Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity

Results of an International Workshop Organized by the Interagency Coordinating
Committee on the Validation of Alternative Methods (ICCVAM)
and the

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

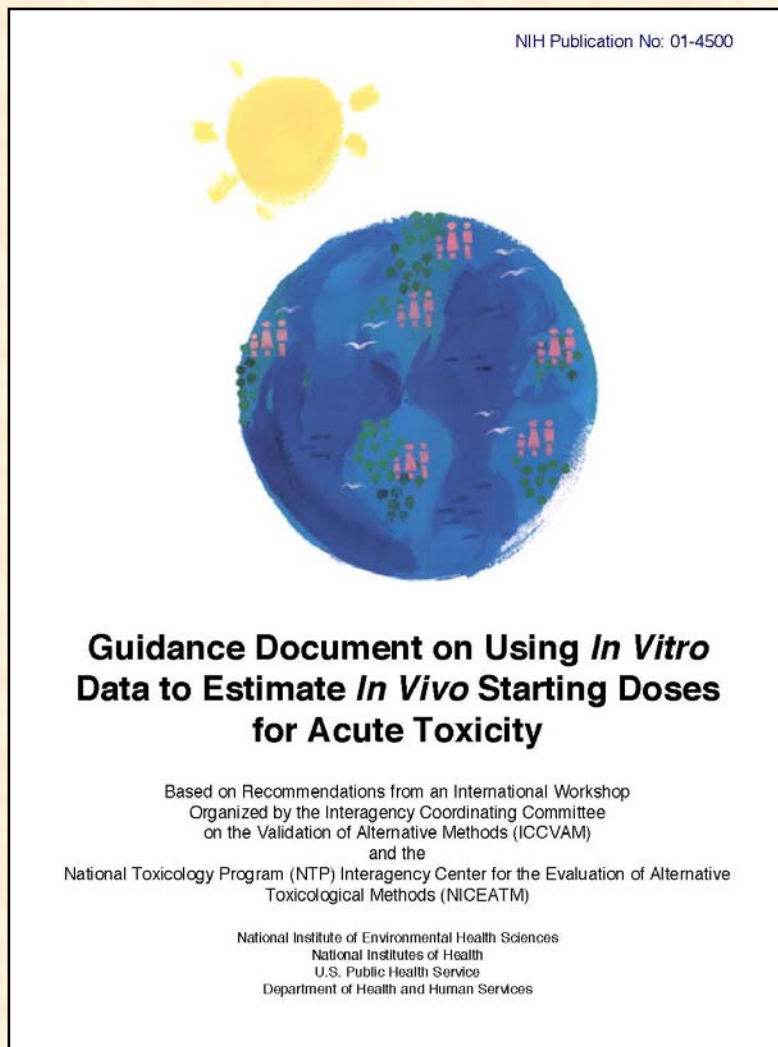
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

- **ICCVAM International Workshop**
- **Recommendations provided for research, development, validation efforts:**
 - **Screening methods**
 - **Toxicokinetic methods**
 - **Target organ toxicity methods**
 - **Chemicals for validation studies**
- **<http://iccvam.niehs.nih.gov>**



Guidance Document: Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity

- Describes how to use cytotoxicity data to estimate relative toxicity and starting doses for acute toxicity studies
- Provides protocols for 2 basal cytotoxicity methods
 - 3T3 and NHK cells
 - Updated protocols now available at NICEATM-ICCVAM website
- Supported by ZEBET and IIVS studies
- <http://iccvam.niehs.nih.gov>



ICCVAM Acute Toxicity Test Method

Recommendations¹: *In Vitro* Methods - 1

- **Recommendations regarding potential current uses**
 - *Cytotoxicity assays can be useful as one of the tools in setting the starting dose for an in vivo assessment of acute oral toxicity*
 - *Using in vitro approaches could reduce animal use for acute toxicity determinations*
 - Up to an additional 40% reduction in animals per test
 - Fewer animals euthanized for severely toxic chemicals
 - *Agencies should consider making this information available as one of the tools that can be used to select an appropriate starting dose for acute oral toxicity tests*

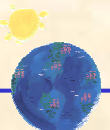
¹ Report of the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity. NIH Pub. No. 01-4499, 2001, NIEHS, Research Triangle Park, NC.



ICCVAM Acute Toxicity Test Method

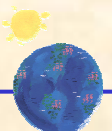
Recommendations: *In Vitro* Methods - 2

- **Research, Development, and Validation**
 - Near-term validation studies should focus on two standard cytotoxicity assays
 - Longer-term activities should be directed at improving *in vitro* systems that provide information on biokinetics, metabolism, and organ-specific toxicity
 - *These will be necessary to facilitate reasonably accurate predictions of LD50s, signs and symptoms associated with toxicity, and pathophysiological effects*



ICCVAM Acute Toxicity Test Recommendations: Non-regulatory responses

- **Concurrence with scientific validity of the UDP**
- **Institutional Animal Care and Use Committees**
 - informed of availability of the UDP and *in vitro* methods
 - *PHS Policy on the Humane Care and Use of Laboratory Animals*:
 - IACUCs must ensure that alternative methods are considered and used where appropriate
- **Agency scientists**
 - informed of availability of both methods
- **Response to research, development, and validation recommendations:**
 - NIEHS and EPA support of validation study on cytotoxicity methods



Alternative Tests for Acute Oral Toxicity: Reduction and Refinement

<u>Test Method</u>	<u>No. of Animals</u>	<u>No. of Deaths</u>	<u>Time to Conduct (in-life)</u>
Original TG 401 (1981)	~ 45	Up to 25	14 days + s.s. ¹
Revised TG 401 (1987)	~ 25	Up to 12	14 days + s.s. ¹
Revised UDP: TG 425 (2001)	6 - 9	0-6 ²	6-30 days ³
Revised UDP + <i>in vitro</i> test	3 - 6	0-3 ²	3-24 days ³

¹S.S.: Sighting study for dose-range finding

²When appropriate for use; no deaths may occur for nontoxic substances; all animals may die for highly toxic substances.

³Shortest duration is for highly toxic substances ($LD_{50} \leq 5$ mg/kg - Category 1); longest duration would result for chemicals with intermediate to no toxicity (Categories 2-5: $5 \leq LD_{50} > 5000$ mg/kg).



NIH Publication No: 03-4508



ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods

Prepared by the
Interagency Coordinating Committee on the
Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program (NTP) Interagency Center for the Evaluation
of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

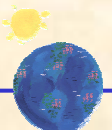
ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods

- Revised version published September, 2003
- *Federal Register*, Nov 2003
 - Announced availability
 - Invited nominations and submissions
- <http://iccvam.niehs.nih.gov>



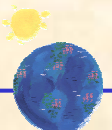
ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods (2003)

- **ICCVAM test method nomination and submission process**
- **ICCVAM Prioritization Criteria**
- **Performance Standards for test methods**
- **Submission guidance for proposed test methods**
- **Outline for organizing nominations and submissions**



ICCVAM Agency Representatives Survey

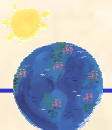
- **Objective:**
Identify testing endpoints that should receive priority for future ICCVAM activities
 - *Consistent with ICCVAM Authorization Act*
 - *Emphasis on opportunities to:*
 - reduce or eliminate pain and distress
 - reduce and/or replace animal use



ICCVAM Regulatory Testing Priorities: Survey Results

	<u>Weighted Score*</u>
1. Acute eye irritation/corrosion	61
2. Acute skin toxicity	
• Dermal irritation/corrosion	48
• Dermal sensitization	24
• Dermal absorption	12
3. Acute systemic toxicity	
• Oral/dermal/inhalation	42
4. Chronic toxicity/carcinogenicity	29
5. Reproductive/developmental toxicity	23

* Priority points: 1st = 5 points; 2nd = 4 points; 3rd = 3 points; 4th = 2 points; 5th - 1 point.



ICCVAM-NICEATM Collaborations with ECVAM (1)

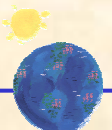
- **International guidance on application of GLPs to *in vitro* toxicity testing**
 - OECD GLP Working Group Task Force on *In Vitro* Studies
 - Task Force meeting in February, 2004
 - Advisory document revised
 - Consideration by the GLP WG in May 2004

- ***ECVAM in vitro* dermal irritation validation study**
 - ICCVAM and NICEATM observers on study management team
 - NICEATM Contributions
 - ID candidate Reference Chemicals
 - ✓ Collaboration with EPA to review 2400 chemicals in the TSCATS database
 - Estimate false negative rates for the rabbit skin test
 - ✓ For current and GHS hazard classification categories



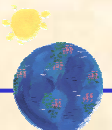
ICCVAM-NICEATM Collaborations with ECVAM (2)

- **ICCVAM-NICEATM-ECVAM Workshop:**
*Validation Principles and Approaches for
Toxicogenomic-based Methods*
 - December 2003, Ispra, Italy
 - Co-chaired by Len Schechtman(FDA, ICCVAM) and Raffaella Corvi (ECVAM)
 - Report and recommendations presented at the next SACATM meeting
- **Workshop on Strategies to Replace In Vivo Acute Systemic Toxicity Testing**
 - September 2003, Ispra, Italy
 - Participation by 4 SACATM and ICCVAM members
 - Report and recommendations presented at the next SACATM meeting



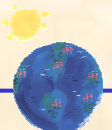
ICCVAM-NICEATM Collaborations with ECVAM (3)

- **Joint validation study on *in vitro* methods for acute toxicity**
 - Phase II completed: September 2003
 - Phase III underway; completion June, 2004
- **Joint participation in upcoming workshops**
 - Weight-of-Evidence Evaluation of Scientific Validity
 - Good cell culture practices



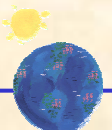
ICCVAM-NICEATM Collaborations with ECVAM (4)

- **Collaborative Evaluation of Ocular Irritation Assays**
 - *In vitro* and refinement alternatives
 - Data sharing; Background Review Document preparation
 - Designated Liaisons
 - ICCVAM Ocular Toxicity Working Group
 - ECVAM Ocular Irritation Task Force



ICCVAM-NICEATM: Other Related Activities

- **ILSI Biomarkers Subcommittee**
 - **Liaison members from ICCVAM and NICEATM**
- **Communications with test method developers**
- **Participation in upcoming scientific meetings**
 - **Society of Toxicology Annual Meeting - March, 2004**



ICCVAM-NICEATM: Society of Toxicology Annual Meeting

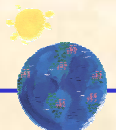
- **Poster Sessions:**

- ICCVAM Process for Nomination and Submission of New, Revised, and Alternative Test Methods (#1811)
- The ICCVAM/NICEATM Process for Developing Test Method Performance Standards (#1812)

- Phase I and II Results of a Validation Study to Evaluate In Vitro Cytotoxicity Assays for Estimating Rodent and Human Acute Systemic Toxicity (#240)
- Data Collection and Analysis Systems for an In Vitro Cytotoxicity Validation Study (#241)

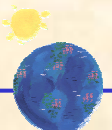
- Estimation of False Negative Rates for the In Vivo Rabbit Dermal Irritation Assay (#1298)
- Estimate of False Negative Rates for the In Vivo Rabbit Dermal Corrosion Assay (#1299)

[All posters available at: <http://iccvam.niehs.nih.gov/>]



ICCVAM-NICEATM: Society of Toxicology Annual Meeting

- **Workshops**
 - Workshop on Assurance of Animal Welfare in Research: Coexistence of Toxicology Studies with Humane Endpoints
 - Workshop on Current Status and Future Considerations for the Development of Skin Toxicology Alternative Methods



ICCVAM 2003 Biennial Report

NIH Publication No: 04-4509

ICCVAM Biennial Progress Report

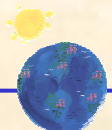


December 2003

Prepared by the
Interagency Coordinating Committee on the
Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program (NTP) Interagency Center for the Evaluation
of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

- **Required by Public Law 106-545**
 - Describes progress made in accordance with the act
- **Final clearance and publication - February 2004**
- ***Federal Register* - 2004**
 - Availability announced
- **<http://iccvam.niehs.nih.gov>**

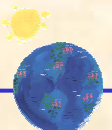


ICCVAM Agency Representatives*

ATSDR	William Cibulas Moiz Mumtaz	FDA	Leonard Schechtman, NCTR (Chair) Suzanne Fitzpatrick, ORA Abigail Jacobs, CDER Raju Kammula, CDRH Melvin Stratmeyer, CDRH Richard McFarland, CBER David Hattan, CFSAN Robert Bronaugh, CFSAN Devaraya Jagannath, CVM M. Cecilia Auguila, CVM William Allaben, NCTR Martha Moore, NCTR Atin Datta, ORA
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USDA	Jodie Kulpa-Eddy Elizabeth Goldentyer		
DOD	Robert E. Foster Patty Decot Harry Salem John Frazier	NCI	Alan Poland Marjorie Strobel
DOE	Marvin Frazier Marvin Stodolsky	NIEHS	William Stokes John Bucher Rajendra Chhabra Jerrold Heindel
DOI	Barnett Rattner Sarah Gerould		
DOT	George Cushmac Steve Hwang	NIOSH	Paul Nicolaysen Douglas Sharpnack
EPA	Joseph Merenda, OSCP Karen Hamernik, OSCP Harold Zenick, ORD Angela Auletta, OPPT Suzanne McMaster, ORD Maurice Zeeman, OPPT	NIH	Margaret Snyder Nelson Garnett
		NLM	Vera Hudson Jeanne Goshorn
		OSHA	Surrender Ahir

* March 2004

ICCVAM
NICEATM



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2004 ICCVAM Strategic Planning Meeting

