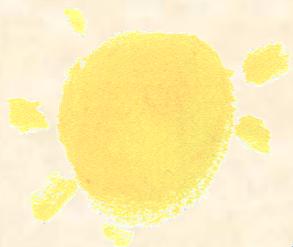


NICEATM

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

ICCVAM

Interagency Coordinating Committee
on the Validation of Alternative
Methods



ICCVAM Nominations

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

**4th Meeting of the Scientific Advisory
Committee on Alternative Toxicological
Methods**

**October 20, 2004
Research Triangle Park, NC**



ICCVAM
NICEATM



Outline

- **Ocular and dermal toxicity test methods/ approaches for antimicrobial cleaning products**
- ***In vitro* endocrine disruptor test methods-update**



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

- **June 21, 2004 letter from Director, EPA Office of Pesticide Programs (OPP):**
 - **EPA's OPP and Pesticide Program Dialogue Committee**
 - **developing non-animal approach for assessing skin and eye irritation potential for antimicrobial cleaning product formulations**
 - **EPA OPP planning a technical workshop to evaluate approach under auspices of the PPDC**
 - **ICCVAM technical review of the approach requested**



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

- **ICCVAM Action**
 - Considered EPA request for ICCVAM review
 - Jack Housenger, and Tina Levine, EPA/OPP, provided overview and information
 - Approved recommendations for involvement



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

ICCVAM recommendations:

- 1. ICCVAM agrees with the EPA Pesticide Program Dialogue Committee (PPDC) that it is important to develop non-animal approaches for evaluating the skin and eye irritation potential and labeling requirements for antimicrobial cleaning product formulations*
 - **Products and ingredients applicable to several ICCVAM agencies**
 - **Consistent with the 2003 EPA nomination of non-animal test methods for ocular irritancy/corrosion**
 - **High priority**



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

ICCVAM recommendations (cont):

- 2. ICCVAM recommends that the most appropriate and efficient means of evaluating non-animal methods for this purpose is to convene an ICCVAM-coordinated independent scientific expert panel with the opportunity for public input.*

The panel would review a background review document [submission] of all available data documenting the accuracy and reliability of these methods/approaches for their intended purpose.



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

ICCVAM recommendations (cont.)

- 3. ICCVAM recommends an open line of communication and a strong working relationship between PPDC, NICEATM and the ICCVAM Ocular/Dermal Working Groups to maximize efficiency and to minimize duplicative efforts.*

Such coordination should expedite the preparation of an adequate Background Review Document for submission, and avoid delays in attaining complete and adequate documentation.



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

4. ICCVAM recommended timeline

Reflects discussions with EPA and PPDC representatives

October 12, 2004:

- ICCVAM Ocular Toxicity and Dermal Corrosivity and Irritation Working Groups: Overview of proposed test methods/ approaches by EPA and PPDC

October 20, 2004:

- ICCVAM recommendations to SACATM for comment

Fall/Winter 2004

- Data collection and preparation of submission by sponsors
- ICCVAM call for data for the proposed test methods/ approaches, and nomination of experts for review panel
- Publication 30 days after EPA/PPDC concurrence with ICCVAM proposal



Ocular/Dermal Test Methods: Antimicrobial Cleaning Products

4. Timeline (cont):

- Expected submission to ICCVAM -April 05
- Open/public ICCVAM independent expert panel meeting
 - ~6 months after submission, e.g., Fall '05
- Post-meeting actions:
 - ICCVAM expert panel report released for public comment
 - ICCVAM expert panel report, public comments, and proposed ICCVAM recommendations presented to the EPA Science Advisory Panel
 - ICCVAM final recommendations to Federal Agencies per P.L. 106-545
 - EPA consideration/ implementation of ICCVAM and SAP recommendations



In Vitro Endocrine Disruptor Test Methods

Update on Nominations



Endocrine Disruptor Test Methods: ICCVAM Recommendations, March 2003

- Preference should be given to development and validation of assays that:
 - Do not require the use of animal tissue/surgical procedures for the receptor source, but rather use recombinant-derived proteins
 - Do not use radioactive materials
- Performance Standards should be developed following validation studies on at least one test method of each type:
 - ER binding
 - ER transcriptional activation
 - AR binding
 - AR transcriptional activation



Previously Nominated Endocrine Disruptor Test Methods

- Biosensor system that can assess estrogen receptor binding and transcriptional activation
- Stably transfected recombinant cell-based ER transcriptional method (*LUMI-CELL*[™])



Endocrine Disruptor Nominations: ICCVAM Recommendations, March 04

- *Evaluation studies for in vitro receptor binding and transcriptional activation test methods that do not require the use of animals should receive a high priority for support.*
- *Prior to the initiation of such studies, the proposed validation studies should be evaluated by the ICCVAM Endocrine Disruptor Working Group (EDWG) and NICEATM for adherence to relevant recommendations in the report:*
 - *ICCVAM Evaluation of In Vitro Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays(NIH Publication No. 03-4503)*



***In vitro* Endocrine Disruptor Test Method Nominations**

- ***Federal Register* notice (69(77): 21564, April 21, 2004)**
 - Requested comments on the two *in vitro* ER assays nominated for validation studies:
 - Stably transfected ER TA (XDS, Inc.)
 - Biosensor system for ER Binding and TA (IA, Inc.)
 - Requested additional nominations of *in vitro* ED test methods that:
 - Do not require the use of animal tissue as the receptor source
 - Do not use radioactive materials
 - Have standardized protocols, pre-validation data, and validation study designs
 - Responses requested by June 7, 2004



***In vitro* Endocrine Disruptor Test Method Nominations**

- **Responses to *Federal Register***
 - **No public comments received on XDS or IA, Inc. assays**
 - **Received notices of intent to nominate and/or preliminary data for 3 test methods**
 - **CertiChem, Inc. - MCF-7 cell proliferation assay (letter of intent and draft submission for comment)**
 - **IRAS, The Netherlands - H295R cell line screening assay (letter of intent and preliminary submission)**
 - **U.S. EPA - Dr. Earl Gray indicated intent to submit ER binding/TA assays for consideration (nothing received to date)**
 - **Data currently under evaluation by NICEATM**



***In vitro* Endocrine Disruptor Test Method Nominations**

- NICEATM evaluated the XDS, Inc. LUMI-CELL™ ER high-throughput assay standardized protocol and data
 - *Protocol adheres to the ICCVAM recommended essential test method components; pre-validation data adequate*
- ICCVAM Endocrine Disruptor Working Group and ICCVAM reviewed and concurred with the NICEATM evaluation and developed the following recommendations:



In vitro Endocrine Disruptor Test Methods

ICCVAM Recommendations:

- 1. LUMI-CELL™ should be given a high priority for validation studies to evaluate its usefulness as an *in vitro* test method for the detection of test substances with *in vitro* ER agonist and/or ER antagonist activity.**
- 2. Independent standardization and a phased validation study should be conducted. The proposed validation study would include the following:**
 - Phase I: 3 laboratories demonstrate proficiency with a standardized protocol for agonist and antagonist activity using a reference estrogen and positive controls and develop a historical positive control database**
 - Phase II: 3 laboratories test a limited number of chemicals to demonstrate intra- and inter-laboratory reproducibility as well as making adjustments to the standardized protocol, if needed.**
 - Phase III: 3 laboratories test the full list of reference chemicals**

Progression from one phase to the next will be dependent upon successful completion of the previous phase.



***In vitro* Endocrine Disruptor Test Methods**

ICCVAM recommendations (cont):

- 3. *Ideally, NICEATM should coordinate the validation studies with the European and Japanese Centers for the Validation of Alternative Methods (ECVAM and JCVAM/NIHS, respectively), and ideally, include one laboratory in each of the three respective geographic regions supported by these three Centers.***
- 4. *Prior to interlaboratory validation studies, XDS should conduct additional antagonist studies to optimize the LUMI-CELL™ assay for the detection of substances with ER antagonist activity.***
- 5. *Following validation studies, ICCVAM should:***
 - *Develop and propose performance standards for ER TA assays***
 - *Conduct a technical evaluation, including independent peer review, of the results of the validation studies***
 - *Develop and forward ICCVAM test method recommendations to Federal agencies***



ICCVAM ED Nominations: Next steps

- SACATM comments on ICCVAM recommendations
- ICCVAM Final Recommendations
- NICEATM request for funding of recommended studies to Director, ETP

