Society of Toxicology - 43rd Annual Meeting
Baltimore, MD
March 21 - 25, 2004
ICCVAM/NICEATM POSTER PRESENTATION ABSTRACT

ID#	**1812**
Location:	Exhibit Hall
Time of Presentation:	March 24, 1:30 PM
Category (Subcategory):	Regulatory/Policy, (*In Vitro*/Alternative Animal Models)

The ICCVAM/NICEATM Process for Developing Test Method Performance Standards

W.S. Stokes[1], L.M. Schechtman[2], A. Rispin[3], R.N. Hill[3], K. Hamernik[3], B.C. Blackard[4], R.R. Tice[4]
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2. FDA, NCTR, Rockville, MD
3. U.S. EPA, Washington, DC
4. ILS Inc., RTP, NC

Test methods proposed for regulatory testing should routinely undergo validation studies to assess their reliability and relevance for specific applications. Regulatory agencies can then determine if the test method is sufficiently accurate and reliable to be accepted for a proposed specific use. The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) has established a process for developing and using performance standards (PS) to evaluate the acceptability of proposed test methods that are based on similar scientific principles and that measure or predict the same biological or toxic effect as an accepted test method. ICCVAM defined the three critical components of PS as: (1) essential test method components, i.e. the requisite structural, functional, and procedural elements of a validated test method that should be included in the protocol of a proposed mechanistically and functionally similar test method; (2) a minimum list of reference chemicals, which is used to assess the accuracy and reliability of the analogous test method; and (3) comparable accuracy and reliability values that should be achieved by the proposed test method when evaluated using the minimum list of reference chemicals. The ICCVAM also established a process for developing and recommending PS during future test method evaluations. NICEATM and an ICCVAM working group will develop proposed test method specific PS, which will be made available for public comment. An independent peer review panel will review the proposed PS for completeness and appropriateness as a part of the panel's evaluation of the proposed test method. ICCVAM will then finalize and forward recommended PS together with test method recommendations to Federal agencies and make these available to the public. The availability of PS is expected to facilitate the development and validation of improved test methods that are similar to previously accepted methods. ILS staff supported by NIEHS contract NO1-ES-35504.

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ICCVAM/NICEATM POSTER PRESENTATION ABSTRACT

ID#	**1811**
Location:	Exhibit Hall
Time of Presentation:	March 24, 1:30 PM
Category (Subcategory):	Regulatory/Policy, (*In Vitro/Alternative Animal Models)*

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

L.M. Schechtman[1], W.S. Stokes[2], M. Wind[3], B.C. Blackard[2, 4], R.R. Tice[2, 4].
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4. ILS, Inc., RTP, NC, USA.

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) coordinates (a) the technical evaluation of new, revised and alternative test methods of Federal agency interest, and (b) cross-agency issues relating to the validation, acceptance and national and international harmonization of toxicological test methods. ICCVAM recently developed and adopted a process by which test method nominations and submissions are considered and prioritized for review and evaluation. Prioritization of proposed test methods is based on several criteria, including: the applicability of the method to regulatory testing needs; the extent of anticipated use by one or more agencies; the level of multi-agency interest; the potential for the method to reduce, refine or replace animal use; the prospect of the test method to provide improved prediction of adverse health or environmental effects compared to current test methods accepted by regulatory agencies; and the extent to which the test method affords other advantages, such as reduced time or cost. The newly revised ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods describe: 1) the ICCVAM nomination and submission process, 2) the information that should be provided in a test method submission or nomination and an outline for organizing the necessary information; and 3) the ICCVAM process for developing performance standards, which communicate the basis on which a validated and accepted test method has been determined to have sufficient accuracy and reliability for a specific testing purpose. Test method submitters/ nominators are encouraged to utilize these Guidelines and communicate with NICEATM and ICCVAM during the preparation of test method submissions and nominations. These Guidelines are expected to facilitate the preparation of test method submissions and nominations and their consideration by ICCVAM. ILS staff supported by NIEHS Contract NO1-ES-35504.

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Society of Toxicology - 43rd Annual Meeting
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ICCVAM/NICEATM POSTER PRESENTATION ABSTRACT

ID#	**240**
Location:	Exhibit Hall
Time of Presentation:	March 22, 9:30 AM
Category (Subcategory):	*In Vitro*/Alternative Animal Models, (Regulatory/ Policy), (Safety Evaluation)

Phase I and II Results of a Validation Study to Evaluate *In Vitro* Cytotoxicity Assays for Estimating Rodent and Human Acute Systemic Toxicity

M.W. Paris[1,2], J.A. Strickland[1,2], W.S. Stokes[1], S. Casati[3], R.R. Tice[1,2], H. Raabe[4], C. Cao[5], R. Clothier[6], J. Harbell[4], G. Mun[4], A. Sizemore[4], G. Moyer[4], J. Madren-Whalley[5], C. Krishna[5], M. Owen[6], N. Bourne[6], J. Haseman[7], P. Crockett[8], M. Wenk[9], M. Vallant[7], A. Worth[3].
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2. ILS, Inc., RTP, NC, USA.
3. ECVAM, Ispra, , Italy.
4. IIVS, Gaithersburg, MD, USA.
5. US Army, APG, MD, USA.
6. Univ. of Nottingham, Nottingham, , UK.
7. NIEHS, RTP, NC, USA.
8. ASI, RTP, NC, USA.
9. BioReliance, Rockville, MD, USA.

Studies have identified a correlation between in vitro cytotoxicity and acute oral toxicity. NICEATM and ECVAM initiated a three-phase multi-laboratory validation study to evaluate the usefulness of two standardized *in vitro* basal cytotoxicity assays for estimating rodent and human acute toxicity and the extent that they may reduce animal use. Seventy-two coded chemicals (12 from each of five acute oral hazard categories; 12 unclassified/nontoxic chemicals) will be tested in mouse 3T3 fibroblasts and in normal human epidermal keratinocytes (NHK) using neutral red (NR) uptake assays. Protocols were optimized after each of the first two phases to minimize intra- and inter-laboratory variation prior to testing 60 chemicals in Phase III. Phase Ia established the historical databases for the positive control chemical, sodium laurel sulfate (SLS), for each of three laboratories. Three chemicals were tested in Phase Ib and nine in Phase II. Technical challenges arose in Phases Ia/Ib (i.e., formation of NR dye crystals; uneven growth of NHKs; slow growth of 3T3 cells) that were resolved with Phase II protocols. Significant variation in NHK growth occurred in Phase II with various lots of media and supplements. The optimized final protocols are being tested in Phase III. Rodent oral LD50 values were estimated using prediction models based on the Registry of Cytotoxicity data and Phase I/II results. Human toxicity will be estimated using a prediction model based on data from human poisoning reports and the Multicentre Evaluation of *In Vitro* Cytotoxicity (MEIC). Supported by: N01-ES-35504, N01-ES-75408; EPA IAG DW-75-93893601-0; European Commission 19416-2002-04 F2ED ISP GB.

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ICCVAM/NICEATM POSTER PRESENTATION ABSTRACT

ID#	**241**
Location:	Exhibit Hall
Time of Presentation:	March 22, 9:30 AM - 12:30 PM
Category (Subcategory):	*In Vitro*/Alternative Animal Models I, (Biological Modeling), (Safety Evaluation)

Data Collection and Analysis Systems for an *In Vitro* Cytotoxicity Validation Study

J.A. Strickland[1], M.W. Paris[1], H. Raabe[2], J.H. Haseman[3], S. Casati[4], R. Clothier[5], C. Cao[6], P. Crockett[7], R.R. Tice[1], W.S. Stokes[3]
1. NICEATM and ILS Inc., RTP, NC
2. IIVS, Gaithersburg, MD
3. NIEHS, RTP, NC
4. ECVAM, JRC, Ispra, Italy
5. University of Nottingham, Nottingham, UK
6. U.S. Army ECBC, APG, MD
7. Analytical Sciences Inc., RTP, NC

NICEATM and ECVAM designed a multi-laboratory validation study to evaluate two *in vitro* basal cytotoxicity test methods using 72 coded chemicals with a wide range of acute oral toxicity. The study was designed in three phases to allow adjustments in the cytotoxicity protocols and data collection and evaluation procedures before the majority of the chemicals are tested in Phase III. An Excel® template was distributed to the participating labs for collection of raw data, analysis for outliers among dose replicates, documentation of materials and procedures, simple graphical analysis of dose-response, and transformation of data to the proper format for further analysis. Rather than applying a linear interpolation technique to the dose response to calculate the IC_{50}, GraphPad Prism® software was used to perform a Hill function analysis. IC_{20}, IC_{50}, and IC_{80} values and associated 95% confidence limits were calculated, and the data and fitted model were graphed. Initial criteria for an acceptable dose-response for individual tests included one data point between 10 & 50% viability, one data point between 50 & 90% viability, and $r^2 \geq 0.8$. A Prism® template was distributed to the laboratories to automate and provide uniformity of analysis. To increase the speed of data collection and evaluation of the analyses by the Study Management Team (SMT) and consulting biostatisticians, the laboratories submitted Excel® and Prism® data files by e-mail. Results compiled by the SMT were returned to the originating laboratories for audit to ensure accurate transmission of data. Implementation of these procedures shows that automated data collection in relatively common, easy-to-use electronic formats can facilitate uniformity of data collection and analysis. Supported by: N01-ES 35504; EPA IAG DW-75-93893601-0; European Commission 19416-2002-04 F2ED ISP GB.

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Society of Toxicology - 43rd Annual Meeting
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ICCVAM/NICEATM POSTER PRESENTATION ABSTRACT

ID#	**1298**
Location:	Exhibit Hall
Time of Presentation:	March 24, 9:30 AM
Category (Subcategory):	*In Vitro*/Alternative Animal Models, (Skin), (Regulatory/Policy)

Estimation of False Negative Rates for the *In Vivo* Rabbit Dermal Irritation Assay

N.Y. Choksi[1,2], R.R. Tice[1,2], J.H. Haseman[3], W.S. Stokes[2]
1. ILS Inc., RTP, NC
2. NICEATM, RTP, NC
3. NIEHS, RTP, NC

Alternative *in vitro* test methods proposed to substitute or replace an *in vivo* test method should provide equivalent or improved protection of human or animal health in order to gain regulatory and general acceptance. The ICCVAM and NICEATM are collaborating with the ECVAM to conduct a validation study of three *in vitro* dermal irritation assays. To assess the acceptability of these *in vitro* assays, an effort was undertaken to estimate the false negative rate of the *in vivo* test as defined by its ability to consistently identify irritants, mild irritants, and non-irritants according to the Globally Harmonized Classification Scheme. Data for 187 substances was obtained from the ECETOC database for skin irritation and corrosion. The distribution of rabbits with mean erythema or oedema scores of <1.5, between 1.5 and 2.3, or >2.3 was determined for each of the substances classified as "negative", "mild irritant" or "irritant". Since the true classification of each substance is unknown, a simplifying assumption was made that the results are correct for substances tested once only. For multiple-tested substances, the classification obtained from a majority of the studies was used. The analysis indicated: (1) the likelihood of a mild irritant being under-classified as a non-irritant was <5% when based on all substances and <10% when based on multiple-tested substances, (2) the under-classification rate of irritants as non-irritants was <1%, and (3) the under-classification rate of irritants as mild irritants ranged from 9-30%, depending on whether all substances or only multiple-tested substances were considered. Additional *in vivo* irritation data for studies using currently accepted procedures was requested from US federal agencies and industry. Appropriate data received will be added to the database and the false negative analysis refined. This evaluation emphasizes the need for high quality *in vivo* dermal irritation data that can be used to assess the performance of proposed new alternative test methods. ILS staff supported by NIEHS contract N01-ES-35504.

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ICCVAM/NICEATM POSTER PRESENTATION ABSTRACT

ID#	**1299**
Location:	Exhibit Hall
Time of Presentation:	March 24, 9:30 AM
Category (Subcategory):	*In Vitro/Alternative Animal Models, (Skin), (Regulatory/Policy)*

Estimate of False Negative Rates for the *In Vivo* Rabbit Dermal Corrosion Assay

R.R. Tice[1,2], N.Y. Choksi[1,2], J. Haseman[3], R. Hill[4], M. Lewis[4], D. Lowther[4], W.S Stokes[2]
1. ILS, Inc., RTP, NC, USA.
2. NICEATM, NIEHS, Research Triangle Park, NC, USA.
3. NIEHS, RTP, NC, USA.
4. EPA, Washington, DC, USA.
5. FDA, College Park, MD, USA.

Alternative *in vitro* test methods proposed to substitute or replace an *in vivo* assay should provide equivalent or improved protection of human or animal health to gain regulatory and general acceptance. ICCVAM evaluated four *in vitro* dermal corrosivity assays as potential replacements for the *in vivo* dermal corrosivity assay. ICCVAM recommended that these assays be used in accordance with the globally harmonized tiered testing scheme in a weight-of-evidence approach. In this approach positive substances could be classified and labeled as corrosives and negative substances are further evaluated in accordance with an internationally accepted testing scheme. This recommendation was based largely on the 12-17 percent false negative rates of the in vitro assays in identifying corrosive substances. ICCVAM concluded that these false negative rates likely exceeded that of the currently used *in vivo* assay and would not provide adequate public health protection. To estimate the likelihood of a false negative result in the *in vivo* assay, the available data was reviewed. Relevant *in vivo* dermal corrosivity data were obtained from federal agencies and the published literature. The database consisted of 50 corrosive substances. Since the true likelihood of a corrosive response for each of the substances in the database was unknown, the sample rate was considered the best estimate of the true positive response rate. Initial analysis of the database indicated that the current *in vivo* dermal corrosivity test has an estimated false negative rate of 5.5 percent. The analysis also suggests that under-classification of a substance would most likely occur only for weak corrosives. NICEATM continues to seek additional high-quality *in vivo* corrosivity data to refine the estimated *in vivo* assay false negative rate. This evaluation emphasizes the need for high quality *in vivo* dermal corrosivity data that can be used to evaluate the performance of proposed alternative assays. ILS staff supported by NIEHS contract N01-ES-35504.

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W10 - Assurance of Animal Welfare in Research: Coexistence of Toxicology Studies with Humane Endpoints

Chairperson(s): Stephen M. Lasley, University of Illinois College of Med, Peoria, IL and Jeffrey I. Everitt, GlaxoSmithKline, Research Triangle Park, NC.

Endorsed by:
Animals in Research
Neurotoxicology Specialty Section

In the performance of toxicology studies, whether for purposes of Product safety testing or identifying mechanisms of toxicant action, it is necessary to incorporate multiple regulatory, scientific, humane, and ethical factors into the use and care of laboratory animals. This Workshop will provide a forum for discussion of these various factors from different vantage points to better inform the audience, particularly with respect to utilization of humane endpoints. These issues are of timely importance because of continually increasing regulatory oversight of animal care and use, and thus this forum will be of broad interest to toxicologists. Consideration of these factors will be addressed from the standpoint of regulatory requirements and the types of data that must be submitted (Schechtman). A veterinary medicine perspective will be presented, highlighting the development of humane endpoints and their use to determine when study interventions are necessary (Stokes). The role of the IACUC will be defined, particularly in the refinement of the project experimental design and optimization of the proposed numbers of animals (Brown). The conduct of toxicology studies will also be presented from the viewpoint of the investigator, who must balance these factors to produce sound and reliable data (Mattsson). The final presentation will provide a European Union perspective, highlighting the manner in which approaches to these animal care issues are addressed differently in those countries, and indicating trends in regulatory oversight that may soon reach North America (Donovan).

Assurance of Animal Welfare in Research: Coexistence of Toxicology Studies and Humane Endpoints - Issues in Toxicity Testing for Regulatory Purposes, Leonard M. Schechtman, U.S. FDA, Rockville, MD.

Assurance of Animal Welfare in Research: Coexistence of Toxicology Studies with Humane Endpoints-Veterinary Medicine and Animal Welfare Issues, William S. Stokes, DHHS/NIH/NIEHS, Research Triangle Park, NC.

The IACUC as a Value-Added Component of Toxicology Research, Marilyn J. Brown, Charles River Laboratories, Wilmington, MA.

Animal Testing: The Dichotomy Between Natural Toxicants in Food and Synthetic Pesticides Points to a Problem, Joel L. Mattsson, Dow AgroSciences LLC, Indianapolis, IN.

European Perspectives on Animal Welfare and Scientific Endpoints in Animal Studies, John C. Donovan, Wyeth Research, Collegeville, PA.

Workshop - Monday, March 22, 9:30 a.m. - 12:00 noon

W14 - Current Status and Future Considerations for the Development of Skin Toxicology Alternative Methods

Chairperson(s): G. Frank Gerberick, Procter & Gamble Company, Cincinnati, OH and Ian Kimber, Syngenta, Macclesfield Cheshire, United Kingdom.

Endorsed by:
Dermal Toxicology Specialty Section*
Regulatory and Safety Evaluation Specialty Section

The need for alternative approaches and in vitro test methods has never been greater than it is today. The continued development of such approaches and use of validated alternatives test methods is an integral part of toxicology in the 21st century.
Collaboration of researchers and external scientific validation organizations such as ICVAAM and ECVAM that were established to provide a mechanism for alternatives test methods validation test methods spearheaded the way forward. Such efforts have led to significant progress in the replacement of animals, reduction in the number used and refinement of in vivo studies. In addition to scientific considerations, significant regulatory challenges lie ahead with the implementation of the 7th Amendment to the European Union Cosmetics Directive, The European Union Chemicals Policy and the United States program on High Production Volume Chemicals. This workshop will focus on the development of alternative approaches and in vitro methods for the evaluation of cutaneous toxicology. It will include detailed discussion on the use of in vitro/in silico and other alternatives methods/approaches used today for the evaluation of skin irritation skin sensitization and skin penetration. The workshop will be introduced by an overview on the use of alternatives in toxicology today and challenges for the future and will close with placing into context the scientific and regulatory challenges relative to societal expectations.

Overview of Alternatives in Toxicology: Recent Progress and Future Opportunities, William S. Stokes, NIEHS, Research Triangle Park, NC.

Application of Alternatives in the Evaluation of Skin Irritation, David A. Basketter, SEAC, Unilever, Sharnbrook, United Kingdom.

Challenges in Development of Alternative Methods to Evaluate Skin Sensitization, G. Frank Gerberick, Procter and Gamble Co., Cincinnati, OH.

Skin Penetration: Current and Future Directions in the Use of Alternative Methods, Robert Bronaugh, U.S. FDA, Laurel, MD.

Societal Expectations on the Use of Alternatives for the Protection of Animals and Humans, Alan M. Goldberg, Johns Hopkins University, Baltimore, MD.

Workshop - Monday, March 22, 1:30 p.m. - 4:30 p.m.