Annual Progress Report

of the

Interagency Coordinating Committee on the

Validation of Alternative Methods

(ICCVAM)

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

National Institute of Environmental Health Sciences
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2001 Annual Progress Report of the

Interagency Coordinating Committee on the Validation of Alternative Methods

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was formally authorized and designated as a permanent committee by the ICCVAM Authorization Act of 2000 (Public Law 106-545), which was signed into law by the President on December 19, 2000. ICCVAM's duties include the technical evaluation of new and alternative testing methods, development of test recommendations based on those technical evaluations, and forwarding recommendations to Federal agencies for their consideration. The ICCVAM also coordinates interagency issues on toxicological test method development, validation, regulatory acceptance, and national and international harmonization. The ICCVAM Authorization Act of 2000 directs ICCVAM to prepare reports on its progress and to make these available to the public. This annual report complies with the requirement for an initial progress report. Future reports will be prepared in accordance with the Act. Information about ICCVAM can be found on the Internet at: **http://iccvam.niehs.nih.gov**.

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ICCVAM Annual Progress Report Highlights

- The murine Local Lymph Node Assay (LLNA) gained international regulatory acceptance by the 30-member countries of the Organisation for Economic Cooperation and Development (OECD). The LLNA, an improved method for assessing allergic contact dermatitis, was the first method evaluated and recommended by the ICCVAM and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). The LLNA is a mechanism-based test method that provides dose-response information, uses fewer animals, and eliminates pain and distress compared to the standard testing method for which it can be substituted.

- ICCVAM and NICEATM completed evaluation of a revised up-and-down procedure (UDP) that can be used in place of the conventional acute toxicity test for hazard identification and classification. The revised UDP was subsequently accepted by the OECD as an internationally harmonized test guideline. The UDP reduces the number of animals necessary for determining acute toxicity compared to the conventional test.

- The *Report of the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity* was published and made available to the public. Recommendations are provided for research, development, and validation efforts necessary to further advance the use of *in vitro* methods for estimating acute toxicity. The report concludes that while *in vitro* methods cannot currently replace animals for acute toxicity testing, they can be used to screen chemicals for their relative toxicity which can aid in reducing the number of animals necessary for acute toxicity testing.

- A *Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity* was developed and published. The guidance document provides standardized protocols for two *in vitro* cytoxicity methods that can be used to estimate the starting doses for *in vivo* acute toxicity studies. Preliminary data suggest that use of the *in vitro* methods can reduce the number of animals required in a procedure by up to 30 percent.

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The ICCVAM Authorization Act of 2000

The ICCVAM Authorization Act of 2000 (Public Law 106-545) was signed into law by the President on December 19, 2000. The law was enacted "to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness." The stated purposes of the ICCVAM are to:

- Increase the efficiency and effectiveness of Federal agency test method review.
- Eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies.
- Optimize utilization of scientific expertise outside the Federal government.
- Ensure that new and revised test methods are validated to meet the needs of Federal agencies.
- Reduce, refine, or replace the use of animals in testing where feasible.

The Act established ICCVAM as a permanent interagency committee composed of the heads or their designees from the following 15 Federal agencies (see Table l):

Agency for Toxic Substances and Disease Registry
Consumer Product Safety Commission
Department of Agriculture
Department of Defense
Department of Energy
Department of Interior
Department of Transportation

Environmental Protection Agency
Food and Drug Administration
National Cancer Institute
National Institute of Environmental Health Sciences
National Institutes of Health, Office of the Director
National Institute for Occupational Safety and Health
National Library of Medicine
Occupational Safety and Health Administration

ICCVAM Functions

The ICCVAM coordinates interagency issues on test method development, validation, regulatory acceptance, and national and international harmonization. The ICCVAM Authorization Act directs ICCVAM to carry out the following duties:

- Coordinate the technical review and evaluation of new and revised test methods of interagency interest.
- Submit ICCVAM test recommendations to each appropriate Federal agency.
- Facilitate interagency and international harmonization of test protocols that encourage the reduction, refinement, and replacement of animal test methods.
- Facilitate and provide guidance on validation criteria and processes.
- Facilitate the acceptance of scientifically valid test methods.
- Facilitate awareness of accepted methods.
- Consider petitions from the public for review and evaluation of new and revised test methods for which there is evidence of scientific validity.
- Make ICCVAM final test recommendations available to the public.
- Prepare reports on the progress of this Act and make these available to the public.

This report briefly reviews the history of ICCVAM and the test method evaluation process used by ICCVAM. This is followed by a description of the activities that have been carried out during

the past year by ICCVAM and the NTP Interagency Center for the Evaluation of Alternative Methods (NICEATM – pronounced ni-see-tum).

History of ICCVAM

An *ad hoc* ICCVAM was established by the Director of the National Institute of Environmental Health Sciences (NIEHS) in September 1994 to develop a report responsive to requirements in the NIH Revitalization Act of 1993, Public Law 103-43. The Act required NIEHS to establish criteria for the validation and regulatory acceptance of alternative testing methods and to recommend a process through which scientifically valid alternative methods could be accepted for regulatory use. The *ad hoc* ICCVAM was comprised of representatives from the 15 agencies that are now represented on ICCVAM. The *ad hoc* ICCVAM published its final report, *Validation and Regulatory Acceptance of Toxicological Test Methods* in 1997. A standing ICCVAM consisting of 14 agencies was established to implement a process by which new test methods of interest to Federal agencies could be evaluated and to coordinate cross-agency issues on the development, validation, acceptance, and national/international harmonization of toxicological test methods. The ICCVAM gained permanent status with enactment of the ICCVAM Authorization Act of 2000.

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

NICEATM was established in 1998 to provide operational support for the ICCVAM and to organize committee-related activities such as peer reviews and workshops for test methods of interest to Federal agencies. NICEATM is a component of the Environmental Toxicology Program in the NIEHS Division of Intramural Research. Its offices are located in Research Triangle Park, North Carolina. NICEATM provides administrative, technical, and scientific support and coordination for ICCVAM, ICCVAM Working Groups, Peer Review Panels, and the Scientific Advisory Committee. These efforts include actions necessary to comply with applicable provisions of the ICCVAM Authorization Act of 2000 (Public Law 106-545) and the NIH Revitalization Act of 1993 (Public Law 103-43).

NICEATM provides a mechanism for interagency communication with test method developers to maximize the likelihood that validation studies generate information needed by agencies to make decisions on the usefulness of new methods. NICEATM reviews and provides accurate

information regarding new test methodologies and information about current best practices for the humane care and use of animals in toxicological research and testing. As resources allow, NICEATM conducts validation studies to evaluate potential new models and systems that may provide improved predictions of chemical toxicity for humans and that may reduce, replace, or refine (less pain and distress) animal use for toxicity testing.

The ICCVAM Test Method Evaluation Process

When adequate information is available for a new test method, peer review panels (Panels) composed of expert scientists from industry, academia, and government, including the international community, are convened. The Panels are charged with developing a scientific consensus on the validation status of the proposed test method, including its usefulness for generating information for specific human health and/or ecological risk assessment purposes. In assessing the validation status of a method, Panels consider available information for a specific test method and evaluate the extent to which established ICCVAM validation and acceptance criteria have been addressed.

Expert workshops and expert panel meetings are convened for test methods where adequate validation studies have not yet been conducted and for other related topics. These workshops and meetings may address the adequacy of current methods for assessing specific toxicities, identify testing areas in need of improved or new methods, evaluate proposed validation studies, evaluate the interim validation status of methods, and/or develop recommendations for research, development, and validation studies needed to further evaluate or improve the usefulness of various test methods.

The deliberations of all Panels and workshops are conducted in public session and opportunity for public comment is provided prior to and during meetings. Published reports of Panel evaluations and ICCVAM recommendations regarding scientific validity and potential acceptability of test methods are forwarded to Federal agencies for their consideration. Each Federal agency then determines the regulatory acceptability of a method according to its statutory mandates (see Figure 1.)

ICCVAM Scientific Advisory Committee

Section 3. (d) of the ICCVAM Authorization Act directs the establishment of a Scientific

Advisory Committee on alternative toxicological methods to advise ICCVAM and NICEATM on ICCVAM activities. To comply with the Act, the NIEHS is in the process of establishing a NIH Federally chartered advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). The SACATM will be composed of knowledgeable representatives as defined in the Act. The committee will meet no less than once per year in public session and meetings and tentative agendas will be announced through the *Federal Register* and other notices.

ICCVAM Test Method Evaluations

ICCVAM evaluated and recommended its first test method, the murine Local Lymph Node Assay (LLNA), in September 1998. Several other methods have been evaluated since that time. While most of these activities were initiated prior to 2001, this section will briefly summarize the current status of the methods and provide an update on actions accomplished during the past year. The reports and information identified in this section are available electronically on the web (URLs are provided) or in hard copy from NICEATM (NIEHS, P.O. Box 12233 MD EC-17, Research Triangle Park, NC 27709; tel: 919-541-2384; fax: 919-541-0947; niceatm@niehs.nih.gov).

The Local Lymph Node Assay

The LLNA is a new alternative test method for assessing allergic contact dermatitis. Following evaluation by an independent scientific peer review panel, the LLNA was accepted by U.S. EPA, FDA, and OSHA. The LLNA reduces and refines animal use compared to the traditional guinea pig test methods for which it substitutes. An advantage over the traditional test is that it also provides dose-response information. The report and a sample protocol developed by the ICCVAM Immunotoxicity Working Group are available on the ICCVAM website at: http://iccvam.niehs.nih.gov/methods/llna.htm.

International Test Guideline

A new internationally harmonized test guideline (Test Guideline (TG) 429) on skin sensitization using the LLNA was accepted by the Organisation for Economic Co-operation and Development (OECD) at the National Coordinators meeting on May 30-June 1, 2001. The validity of the new guideline was supported by the report of the

independent scientific peer review evaluation of the LLNA coordinated by ICCVAM and NICEATM. The draft test guideline and related information may be found at the OECD website at http://www.oecd.org//ehs/test/pdf429.pdf.

Implementation Workshop

ICCVAM in partnership with the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute's (HESI) Alternatives to Animal Testing Technical Committee organized a training workshop for the LLNA on January 25-26, 2001, at the National Institutes of Health Natcher Conference Center in Bethesda, Maryland. The primary objective of the workshop was to train regulatory scientists and industry toxicologists on how to perform the LLNA and interpret data in accordance with regulatory testing requirements. The specific goals of the workshop were to:

- Provide an overview of the methods, applications, strengths and weaknesses of the LLNA.
- Provide information on the procedures for conducting the assay and interpreting the resulting data in accordance with regulatory testing requirements and guidelines.
- Provide an opportunity for regulatory scientists to become familiar with data generated by the LLNA.
- Provide a forum for scientists to share information on the appropriate use of assay results in hazard, safety, and risk assessments.

Skin Corrosivity

Corrositex^{R}, an *in vitro* method for assessing the dermal corrosivity potential of chemicals, was reviewed by an independent scientific peer review panel in 1999. The Panel concluded that the method could be used to assess the corrosivity potential of certain chemical classes and could be used in a tiered approach for the testing of some additional chemical classes. When used in this manner, the method provides for the refinement, reduction, and partial replacement of animal use. The final peer review report was published in 1999 and acceptance by regulatory agencies was announced in 2000. The peer review report is available on the Internet at: http://iccvam.niehs.nih.gov/docs/reports/corprrep.pdf. A test guideline will be proposed to the OECD Test Guidelines Program in 2002.

Other In Vitro Corrosivity Methods

The European Centre for the Validation of Alternative Methods (ECVAM) recently completed validation studies on three alternative *in vitro* test methods for assessing skin corrosivity – EpiDerm ™, EPISKIN ™, and the Rat Skin Transcutaneous Electrical Resistance (TER) assay. These have been accepted by the European Commission and are now being evaluated by ICCVAM using an expedited review process. This expedited process should accelerate interagency consideration of these test methods, thereby avoiding duplication of effort and unnecessary delays in recommending useful test methods to Federal agencies in accordance with Public Law 106-545.

EpiDerm ™ and EPISKIN ™ utilize a three-dimensional tissue culture model of human skin comprised of a reconstructed epidermis and a functional stratum corneum. The test chemical is applied and cell viability assessed over a defined exposure period. The Rat Skin TER assay measures the extent to which a chemical alters the transcutaneous electrical resistance of a skin disc during a defined exposure period.

The Background Review Document and proposed ICCVAM recommendations for these three methods were made available for public comment in a *Federal Register* notice (Vol. 66, No. 189, pp. 49686-49687, Sept. 28, 2001) and are available on the Internet at: http://iccvam.niehs.nih.gov/methods/epiddocs/epis_brd.pdf.

Up-and-Down Procedure for Acute Oral Toxicity

An independent Peer Review Panel (Panel) meeting was convened in July 2000 to evaluate the validation status of a revised Up-and-Down Procedure (UDP) for assessing acute oral toxicity. The revised UDP was proposed as a replacement for the existing conventional LD50 test (EPA OPPTS 870.1100; OECD TG 401) used to evaluate the acute oral toxicity potential of chemicals for hazard classification and labeling purposes. The Panel concluded that the revised UDP Primary Test, compared to current conventional LD50 tests, provided an improved estimate of acute oral toxicity with a reduction in the number of animals used. The Panel concluded that the revised UDP Limit Test should be accepted as a replacement for the current TG 401 Limit Test. The Panel recommended that the proposed UDP Supplemental Test for slope and confidence interval undergo additional development prior to further consideration. The Panel also recommended minor revisions to the UDP test method guideline and development of a

comprehensive computational software program that would facilitate use of the new method. The EPA developed a software program to aid in dose selection, test-stopping decisions, calculation of an estimated LD50, and calculation of a confidence interval around the LD50. The EPA software program and a revised UDP test guideline were reviewed by the Panel in August 2001. The Panel concluded that the revised UDP test method guideline, including the proposed procedure for calculating the confidence interval for the estimated LD50, and the software program were acceptable and recommended their use for acute toxicity testing. Results of the peer review were used to develop an internationally harmonized UDP Test Guideline for the 30 member countries of the OECD. Minutes of the Panel meetings and materials reviewed by the Panel may be found the ICCVAM/NICEATM website at: http://iccvam.niehs.nih.gov/methods/udp.htm. The final UDP report and ICCVAM test recommendations will be available in early 2002.

Training Workshop on Acute Toxicity Test Methods

ICCVAM, in partnership with the U.S. EPA and ILSI, is organizing a training workshop on Acute Toxicity Testing Methods. The Workshop will provide practical information and case studies to facilitate understanding and the implementation of the UDP and other *in vivo* and *in vitro* alternative methods for acute toxicity. The workshop will be held February 19-21, 2002, at the NIH Natcher Conference Center in Bethesda, Maryland. Additional registration and program information will be available in the near future on the ICCVAM/NICEATM website at: http://iccvam.niehs.nih.gov.

FETAX

An Expert Panel Meeting was convened in May 2000 to evaluate the validation status of the Frog Embryo Teratogenesis Assay—*Xenopus* (FETAX), a screening method proposed for evaluating the developmental toxicity potential of chemicals. The Panel recommended ways to improve the reproducibility and accuracy of the FETAX protocol. They also recommended additional research and test method development that might improve the usefulness of FETAX for predicting developmental toxicity to humans and environmental species. Minutes of the meeting may be found on the ICCVAM/NICEATM website at: http://iccvam.niehs.nih.gov/methods/fetax.htm. A comprehensive technical report will be published in 2002.

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

ICCVAM and NICEATM organized an International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity that was held October 17-20, 2000, in Arlington, Virginia. The goals of the workshop were to assess the current validation status of *in vitro* test methods for evaluating the acute systemic toxicity potential of chemicals, recommend validation efforts necessary to further characterize existing methods, and to identify research and development needed to further improve the usefulness of *in vitro* methods for acute toxicity. Four major topics were discussed: *in vitro* screening methods for assessing acute toxicity; *in vitro* methods for toxicokinetic determinations; *in vitro* methods for predicting organ-specific toxicity; and chemical data sets for validation of *in vitro* acute toxicity test methods. The final Workshop Report and a Guidance Document that describe how *in vitro* methods can be used to estimate the starting dose for animal acute toxicity studies were published in September 2001. These documents are available on the ICCVAM/NICEATM website at: http://iccvam.niehs.nih.gov/methods/invitro.htm. The availability of both reports and a request for public comment were announced in a recently published *Federal Register* notice (Vol. 66, No. 189, pp. 49686-49687, Sept. 28, 2001) which can be viewed at: http://iccvam.niehs.nih.gov/docs/FR/6649686.htm.

***In Vitro* Endocrine Disruptor Screening Methods**

ICCVAM and NICEATM are planning an Independent Peer Review Panel meeting to assess the status of several *in vitro* assays proposed for use in the U.S. EPA's Endocrine Disruptor Screening Program (EDSP). Chemical substances may alter natural endocrine processes in the body by binding with estrogen and/or androgen receptors and either initiating or inhibiting sex hormone dependent gene activation. Because of increased concern about the presence of such substances in food and water, screening assays are being developed to identify substances that may have the potential to disrupt endocrine dependent processes and that should therefore undergo further definitive testing to determine dose-related effects. The proposed estrogen and androgen receptor binding and transcriptional activation assays are relevant for screening purposes because they are relatively sensitive, rapid, and inexpensive. NICEATM is currently preparing background review documents (BRDs) on estrogen receptor and androgen receptor binding and transcriptional activation assays. The documents will provide comprehensive reviews of available data and related information necessary to evaluate the status of these assays. A request for data and nominations of expert scientists to serve

on the peer review panel that will evaluate these *in vitro* endocrine disruptor screening methods was announced in a *Federal Register* notice (Vol. 66, No. 57, pp. 16278-16279, March 23, 2001; http://iccvam.niehs.nih.gov/methods/endocrine.htm.

The Peer Review Panel meeting is scheduled for May 21-22, 2002, in Durham, North Carolina. Details of this meeting will be announced in an upcoming *Federal Register* notice and posted on the ICCVAM/NICEATM website at: http://iccvam.niehs.nih.gov/methods/endocrine.htm.

Related International Activities

International Symposium on Regulatory Testing and Animal Welfare

Several ICCVAM agency representatives participated in the first International Symposium on Regulatory Testing and Animal Welfare, which was held in Quebec City, Canada, on June 21-23, 2001. NIEHS, FDA, and EPA were cosponsors of the meeting. One hundred and sixty experts from 22 countries in North and South America, Europe, and Asia participated. The experts included representatives from national research and regulatory agencies, universities, and industry involved in chemicals, pesticides and drug safety testing. Representatives from European, Canadian, and U. S. animal welfare groups also participated.

The main objective of the Symposium was to develop or identify best practices to minimize or eliminate pain and distress for animals used in safety evaluation and testing procedures. Another objective was to find ways to improve communications among regulated industry, animal welfare enforcement authorities, and regulatory authorities that require safety evaluation and toxicity testing. Breakout Groups discussed and agreed on available best practices that should be implemented now for reducing, replacing, and refining animal use (the Three Rs). The Breakout Groups focused on acute local and systemic toxicity testing, subchronic and chronic toxicity and carcinogenicity testing, the use of non-rodent species in testing, animal care practices, safety and potency evaluations of biologicals, and animal use oversight.

Proceedings will be published in the Spring 2002 issue of the *Institute of Laboratory Animal Research Journal*, a publication of the U.S. National Academy of Sciences. Further information about the Symposium can be found at the following URL: http://www.ccac.ca.

International Conference and Guidance Document on Validation and Regulatory Acceptance

In response to a series of issues about validation of new test methods raised by the OECD, ICCVAM developed extensive comments for use by U. S. delegations to recent OECD meetings. As recommended by ICCVAM, an international conference is being convened by the OECD to address validation and regulatory acceptance issues. The conference will be held in Stockholm, Sweden, on March 6-8, 2002. ICCVAM is represented on the Conference Organizing Committee and several ICCVAM representatives have been invited to serve as discussion leaders and rapporteurs. ICCVAM publications have also been identified as key discussion documents.

ICCVAM also provided extensive comments on a recent OECD *Draft Guidance Document on the Development, Validation, and Regulatory Acceptance of New and Updated Internationally Acceptable Test Methods in Hazard Assessment*. These comments will be distributed to the Conference participants and considered during revision of the document. A copy of ICCVAM's comments may be obtained by contacting NICEATM.

ICCVAM/NICEATM Website

The ICCVAM/NICEATM website has evolved into a vital source of information related to ICCVAM activities. Over the past year, the website has been updated to ease navigation, provide more information to the public, and assure compliance with Section 508 standards. (Note: Section 508 is a part of the Rehabilitation Act of 1973 which requires that electronic and information technology developed, procured, maintained, or used by the Federal government be accessible to people with disabilities.) General overviews of these updates are provided below.

Updated Website

In June 2001, the newly revised ICCVAM/NICEATM website was made public. This new website allows visitors to access any information about ICCVAM or NICEATM within three mouse-clicks of the home page. Navigation bars were added to all pages to facilitate navigation to all major sections of the website. Additionally, all pages were remade to comply with Section 508 standards.

The efficiency of the new website is shown by the decline in the number of times visitors accessed the home page. Analysis of the web statistics indicated that the reduction in the number of times the website was accessed was due to easier navigation within the site. From July 2001 through September 2001, the average number of hits per month was 5,200. After the publication of the *Federal Register* notice on September 28, 2001, which requested public comment on the *In Vitro* Workshop Report and Guidance Document, the number of hits per month increased by 235% for the months of October and November 2001 (average of 13,900). This indicates a high level of public interest in the website.

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◊Jeanne Goshorn, M.S.

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* Principal Agency Representative
◊ Alternate Principal Agency Representative

ICCVAM Test Method Evaluation Process

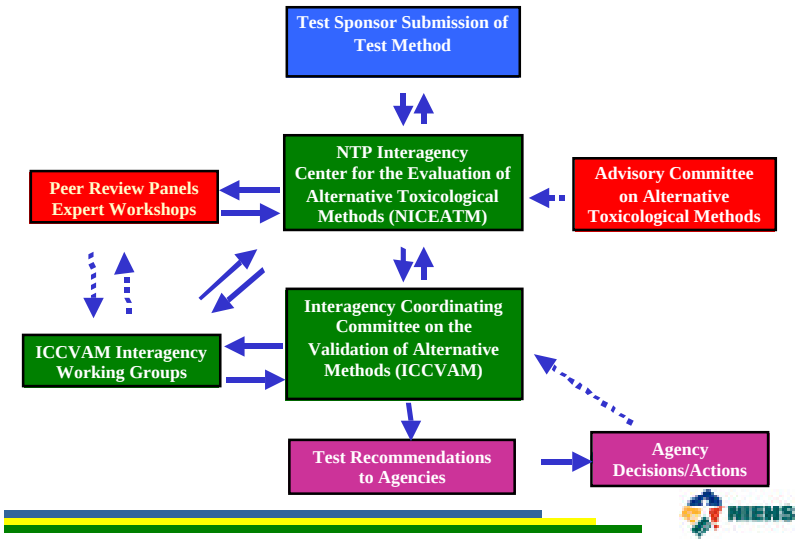

Figure l.