

Minutes from the October 2004 SACATM Meeting

I.	Attendance	2
II.	Call to order and Introductory Remarks	3
III.	NICEATM-ICCVAM Update	3
	A. Test Method Evaluation Activities	3
	B. OECD Test Guideline Program	5
	C. ICCVAM-NICEATM Collaborations with ECVAM	5
	D. SACATM Discussion	6
IV.	ECVAM Update.....	7
	A. Validation Study on <i>In Vitro</i> Methods for Acute Skin Irritation	7
	B. Biologicals and Ecotoxicology Activities.....	8
	C. Workshops	9
	D. Consultations Meetings.....	9
	E. SACATM Discussion	9
V.	Evaluation of the Under-Prediction Rate for the <i>In Vivo</i> Rabbit Dermal Irritation Test.....	10
	A. Introduction.....	10
	B. Data Analysis	11
	C. Public Comment.....	11
	D. SACATM Discussion	12
VI.	Preliminary Evaluation of the Under-Prediction Rate for the <i>In Vivo</i> Rabbit Ocular Irritation Test	13
	A. Introduction.....	13
	B. Data Analysis	14
	C. Public Comment.....	15
	D. SACATM Discussion	16
VII.	ICCVAM Nominations	16
	A. Ocular and Dermal Toxicity Test Methods and Approaches for Antimicrobial Cleaning Products	17
	B. <i>In Vitro</i> Endocrine Disruptor (ED) Test Methods Update.....	17
	C. Public Comment.....	18
	D. SACATM Discussion	18
VIII.	Toxicology in the 21 st Century: A road map for the national toxicology program	21
	A. Roadmap Retreat.....	21
	B. Public Comment.....	22
	C. SACATM Discussion	23
IX.	ICCVAM Perspectives on THE Proposed OECD Draft Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (Guidance Document 34)	24
	A. Meetings and Guidance Documents	24
	B. SACATM Discussion	26
X.	General Discussion	26

Attachment 1: Federal Register Meeting Announcement

Attachment 2: Agenda

Attachment 3: Roster of SACATM Members

Attachment 4: Primary ICCVAM Representatives

Minutes from the October 2004 SACATM Meeting

I. ATTENDANCE

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on October 20, 2004, at the Environmental Protection Agency (EPA), 109 TW Alexander Drive, Research Triangle Park, North Carolina.

SACATM Members in Attendance

Rodger Curren, Ph.D.
Nancy Flournoy, Ph.D.
Alan Goldberg, Ph.D.
A. Wallace Hayes, Ph.D.
Nancy Monteiro-Riviere, Ph.D.
Jacqueline Smith, Ph.D.
Carlos Sonnenschein, Ph.D.
Martin Stephens, Ph.D.
Katherine Stitzel, D.V.M.
Peter Theran, V.M.D.
Calvin Willhite, Ph.D.

ICCVAM Ex Officio Members in Attendance

George Cushmac, Ph.D. (DOT)
Jodie-Kulpa-Eddy, Ph.D. (USDA)
Joseph Merenda, (EPA)
Leonard Schechtman, Ph.D. (FDA)
Margaret Snyder, Ph.D. (NIH)
William Stokes, D.V.M. (NIEHS)
Marilyn Wind, Ph.D. (CPSC)

Liaison Representative in Attendance

Marlies Halder, Ph.D., ECVAM

NIEHS Staff in Attendance

Dave Allen
Brad Blackard
John Bucher, Ph.D.
Neepa Choi, Ph.D.
Sally Fields
Joseph Haseman, Ph.D. (Retiree)
Jerrold Heindel, Ph.D.
Debbie MCarley
William Mundy

Michael Paris
Christopher Portier, Ph.D.
William Schrader, Ph.D.
Judy Strickland, Ph.D.
Raymond Tice, Ph.D.
Kristina Thayer, Ph.D.
James Traux
Mary Wolfe, Ph.D.

Other Federal Staff in Attendance

Marc Jackson (FDA)
Suzanne McMaster (EPA)

Brad Schultz (EPA)

Public in Attendance

Sara Amundson
George Clark, Ph.D.
Sadhana Dhruvakuma
John Gordon, Ph.D.
Sue Leary

Daniel Marsman, D.V.M., Ph.D.
Pauline McNamee
Jim Sherman
Sherry Ward, Ph.D.
Errol Zeiger, Ph.D.

Background materials and presentations for the SACATM meeting are available on the SACATM meeting web site (<http://ntp-server.niehs.nih.gov/ntpweb/index.cfm?objectid=652555EC-F1F6-975E-792DD9BEF9BE0190>). The meeting was broadcast through the Internet and the public was provided opportunity to comment in person or over the phone at designated time points. The meeting was taped for preparation of summary minutes.

II. CALL TO ORDER AND INTRODUCTORY REMARKS

Dr. Kathy Stitzel, acting Chair¹, called the meeting to order at 8:30 a.m. on October 20, 2004, and asked individuals in the room to introduce themselves and provide their affiliation.

Dr. Christopher Portier, Associate Director of the National Toxicology Program (NTP), welcomed SACATM and the Interagency Coordinating Committee on Alternative Methods (ICCVAM) and thanked them for attending the meeting. He also thanked Dr. Stitzel for agreeing to act as chair in the absence of Dr. Jack Dean, the designated SACATM Chair.

Dr. Schechtman, ICCVAM Chair, welcomed SACATM on behalf of ICCVAM. He acknowledged the efforts of ICCVAM principle representatives, alternates, and other agency staff engaged on ICCVAM activities. Dr. Schechtman also thanked NICEATM staff and Integrated Laboratory Systems (ILS) contract staff for providing the scientific, administrative and operational support for ICCVAM.

Dr. Kristina Thayer read the conflict of interest statement for SACATM and reminded everyone present to sign-in and register to present public comments, if applicable. She announced that appointment terms for approximately half of SACATM would expire on June 30, 2005, and encouraged those present to submit nominations for new members.

III. NICEATM-ICCVAM UPDATE

Dr. Stokes, NICEATM Director and ICCVAM Executive Director, welcomed everyone and thanked SACATM for its advice. Dr. Stokes provided an overview of ICCVAM and NICEATM activities since the March 2004 SACATM meeting.

A. Test Method Evaluation Activities

Dr. Stokes discussed activities related to five test methods currently undergoing evaluation.

1. Ocular Toxicity

NICEATM staff and members of the ICCVAM Ocular Toxicity Working Group (OTWG) are preparing background review documents for four *in vitro* methods used to screen for severe/irreversible ocular irritation and corrosion: (1) Bovine Corneal Opacity and Permeability (BCOP) Test, (2) Hen's Egg Test on Chorioallantoic Membrane (HET-CAM), (3) Isolated Rabbit Eye (IRE) Test, and (4) Isolated Chicken Eye (ICE) Test. The Environmental Protection Agency (EPA) nominated these methods for evaluation of their validation status in August 2003. A request for public comment on the nomination of these and other ocular toxicity test methods and a request for data on chemicals evaluated by *in vitro* or *in vivo* ocular irritancy test methods was published in the Federal Register on March 24, 2004 (Vol. 69, No. 57, pp. 13859-13861). NICEATM received five responses to this notice including two that provided *in vivo* data. No additional methods for identifying severe/irreversible ocular effects other than the four named above were identified in response to the notice.

An expert panel of approximately 24 members will review the utility of these methods at a public meeting scheduled for January 11-12, 2005. NICEATM solicited the nomination of scientific experts to serve on the panel in an April 21, 2004 Federal Register notice and received 67 nominations. Dr. Stokes expects the final expert panel report to be distributed in April 2005. NICEATM will announce the report's availability and a request for public comments on it in the

¹ Dr. Stitzel was acting as Chair for the meeting due to the absence of the SACATM Chair, Dr. Jack Dean.

Minutes from the October 2004 SACATM Meeting

Federal Register at that time. Following the public comment period, ICCVAM will consider the report, public comments and comments from SACATM prior to finalizing its recommendations.

In May 2005, ICCVAM and NICEATM will organize two symposia related to ocular toxicity: Mechanism of Chemically-Induced Ocular Injury and Recovery (May 10-11, 2005), and Human Approaches to Ocular Irritancy Testing (May 12, 2005).

2. Endocrine Disruptors

NICEATM is conducting pre-screen evaluations for two endocrine test methods. The first is the LUMI-CELL™ Estrogen Receptor (ER) Screening Assay nominated by XDS, Inc. in January 2004. The submission has been evaluated by NICEATM and the ICCVAM Endocrine Disruptor Working Group (EDWG). NICEATM is currently reviewing pre-validation data submitted by the Otsuka Pharmaceutical Company, Ltd. on an androgen receptor transcriptional activation (AR TA) assay for possible study nomination.

3. Biomarkers

Working groups of the International Life Sciences Institute Health and Environmental Sciences Institute (ILSI HESI) Biomarkers Committee requested input from ICCVAM on validation study plans for three biomarkers of systemic toxicity: (1) inhibin B as a biomarker of testicular toxicity, (2) serum cardiac troponins as markers of cardiac toxicity, and (3) nephrotoxicity biomarkers. To date, the inhibin B study plan has been submitted to the ICCVAM Biomarkers Working Group and the other two are expected to be submitted in the near future.

4. Acute Systemic Toxicity – NICEATM/ECVAM In Vitro Cytotoxicity Validation Study

Dr. Stokes expects the phase III lab testing component of the NICEATM/ECVAM *in vitro* cytotoxicity validation study will be completed in December 2004. The next steps and estimated timeframes are to obtain the final laboratory reports (February 2005), develop background review documents and disseminate the materials for public comment (August 2005), and organize a peer-review (October 2005). A Federal Register notice published on October 19, 2004, announced the availability of optimized and standardized cytotoxicity protocols used to estimate a starting dose for acute systemic *in vivo* toxicity studies; these protocols were optimized as a result of the phase I and II validation studies. NICEATM is also requesting relevant *in vitro* and *in vivo* data that can be used to further evaluate the validity of this approach in reducing animal use.

5. Dermal Toxicity

NICEATM and the ICCVAM Dermal Corrosivity and Irritation Working Group (DCIWG) are currently represented on the study management team for the ECVAM Dermal Irritation Validation Study as observers. NICEATM has contributed to this study by evaluating Toxic Substances Control Act Test Submissions (TSCATS) and Cosmetic Ingredient Review reports to identify candidate reference chemicals for the phase II of the study. To date, NICEATM staff has identified 42 commercially available chemicals with individual animal data; however, purity information is not available for 30 of the 42 chemicals. An important issue in the ECVAM validation study is the finding that several corrosive chemicals tested negative (“false negatives”) in certain *in vitro* test methods [Corrositex, the Rat Skin Transcutaneous Electrical Resistance (TER) Assay, and EPISKIN™/EpiDerm™]. None of these chemicals are currently included in the validation study and the DCIWG has recommended that a series of corrosive chemicals, including all those that tested false negative in the *in vitro* tests, be included in the validation study. The ECVAM management team also considered this issue important and these chemicals will be evaluated in a post-validation study. The DCIWG is working with NICEATM to develop a study design to test false negative corrosive chemicals including preparing a list of chemicals to be tested.

Dr. Stokes noted that NICEATM issued a Federal Register notice on May 28, 2004 (Vol. 69, No. 104, pp. 30693-30694), announcing availability of the ICCVAM-NICEATM document “Recommended Performance Standards for *In Vitro* Test Methods for Skin Corrosion.” These

standards can be used to evaluate test methods similar to the test methods that have already been validated.

B. OECD Test Guideline Program

Dr. Stokes provided a brief overview of current activities of the Organisation for Economic Co-operation and Development (OECD) Test Guidelines Program and noted that ICCVAM and NICEATM are contributing to document. The OECD program is important because it is the primary route to achieving international harmonization for proposed new test methods. Dr. Stokes mentioned that ICCVAM had provided comments on three draft OECD Test Guidelines (TG): Draft OECD TG 435 (*In Vitro* Membrane Barrier Test Method for Skin Corrosion), Draft OECD TG 434 (Acute Dermal Toxicity – Fixed Dose Procedure), and Draft OECD TG 433 (Acute Inhalation Toxicity – Fixed Concentration Procedure). The Draft OECD TG 435 was submitted by ICCVAM to the OECD in February 2003, circulated for comments by the OECD to the National Coordinators (NC) for member countries in May 2004, and may be adopted as a test guideline as early as 2005. OECD TG 435 would be the first test guideline to incorporate performance standards. ICCVAM also submitted comments on draft OECD TG 434 and 433 that were circulated by the OECD to the NC in May and June 2004, respectively.

The OECD Test Guideline Program has also organized two task forces to address *in vitro* issues. The OECD Good Laboratory Practices (GLP) Working Group Task Force on *In Vitro* Studies is charged with developing international guidance on the application of GLPs to *in vitro* toxicity testing. This task force met in February 2004 and finalized an advisory document that was approved by the GLP working group in May 2004 pending consideration by the OECD Joint Meeting in November 2004.

The OECD Non-Animal Testing Validation Management Group for the Task Force on Endocrine Disruptors Testing and Assessment (EDTA) functions to provide advice and coordination for related international validation studies on non-animal endocrine disruptor testing methods. The second meeting for this management will occur on November 2-4, 2004, and one ICCVAM-NICEATM representative (Dr. Stokes) has been nominated as a member of the U.S. delegation.

C. ICCVAM-NICEATM Collaborations with ECVAM

Dr. Stokes discussed five ICCVAM-NICEATM-ECVAM activities from the past year:

1. *ECVAM In Vitro Dermal Irritation Validation Study*. ICCVAM and NICEATM representatives serve as observers on the study management team. In addition, ICCVAM and NICEATM have contributed by identifying candidate reference chemicals for the validation studies and by estimating under-classification rates for the rabbit skin test.
2. *ICCVAM-NICEATM-ECVAM Workshop on Validation Principles and Approaches for Toxicogenomic-based Methods*. This workshop took place in Ispra, Italy in December 2003. Dr. Stokes expects the workshop report and recommendations to be presented to SACATM at the next meeting.
3. *ICCVAM-NICEATM-ECVAM Workshop on Strategies to Replace In Vivo Acute Systemic Toxicity Testing*. Four SACATM members and the NICEATM Director attended the September 2003 workshop held in Ispra, Italy. The workshop report is in press and will be presented to SACATM at the next meeting.
4. *Joint Validation Study on In Vitro Methods for Acute Toxicity*. Laboratory studies for this effort are being conducted in the United States and the United Kingdom and will be completed in December 2004. Dr. Stokes expects the review to occur in 2005. He emphasized the importance of conducting and coordinated validation studies internationally to ensure that a test method is transferable around the world. Future

Minutes from the October 2004 SACATM Meeting

collaborations are expected with the newly developed Japanese Center for the Validation of Alternative Methods (JCVAM).

5. *Collaborative Evaluation of Ocular Irritation Assays.* ICCVAM-NICEATM-ECVAM are working together to prepare background review documents and coordinate future expert panel review of these documents.

Dr. Stokes briefly mentioned that a mini-monograph will be submitted to *Environmental Health Perspectives* summarizing a conference on genomics and alternatives to animal use held during June 2004 in the Netherlands (sponsored by the Netherlands Center for Alternatives and the Netherlands Center for Genomics). Also, he mentioned two upcoming scientific meetings where ICCVAM-NICEATM are participating: (1) The Society of Toxicology Annual Meeting in March 2005 including two workshops on alternatives to ocular irritation and on human approaches to toxicity testing and (2) the 5th World Congress on Alternatives and Animal Use in the Life Sciences in August 2005. The latter meeting is co-sponsored by NIH and NIEHS. Dr. Stokes closed by recognizing the important contributions of ICCVAM agency representatives and NICEATM staff.

D. SACATM Discussion

Dr. Curren commented on the importance of having a workshop or symposium on mechanisms of ocular irritation such as the “Mechanism of Chemically-Induced Ocular Injury and Recovery” (May 10-11, 2005) symposium discussed by Dr. Stokes and asked for additional information. Dr. Stokes said that currently the date of the meeting is the only information available, although the organizing committee for this workshop will be meeting soon. Dr. Stokes also invited the submission of names of experts working in this area to participate in the symposium. The purpose of the symposium will be to assess what is currently known about ocular injury and biomarkers of ocular injury to identify candidate biomarkers that should be considered for incorporation into test methods to potentially enhance their accuracy. Dr. Curren offered the support of his company to help co-organize the meeting (Institute for In Vitro Sciences, Inc.). Dr. Goldberg also offered the assistance of the program he directs, the Center for Alternatives to Animal Testing (CAAT), in organizing and conducting the symposium.

As follow up to discussions at the March 2004 SACATM meeting, Dr. Goldberg asked if there had been any effort to catalogue which programs would have the largest impact on animal use to help determine future priorities. Dr. Stokes replied that in response to advice provided by SACATM, ICCVAM has added potency testing for biologics to the list of ICCVAM-identified priority areas presented at the last meeting. He also commented that ICCVAM, when appropriate, will be involved in reviewing alternatives on veterinary *Leptospira* vaccine potency testing (which accounts for the majority of animals that experience unrelieved pain and distress under USDA reporting guidelines) presented by Dr. Jodie Kulpa-Eddy at the March 2004 SACATM meeting.

Dr. Curren asked if there is any indication whether researchers are incorporating the acute systemic toxicity recommendations of using the *in vitro* methods to set the dose range for *in vivo* testing. Dr. Stokes replied that the EPA’s High Production Volume web site provides a form for submitting this information and encourages data submission. However, to date, NICEATM has received only one submission, and Dr. Stokes is not sure if this reflects a lack of use of the methods or a lack of the reporting of use. For this reason, NICEATM included a request for the submission of *in vitro* and *in vivo* acute systemic data in a March 10, 2004 Federal Register notice [Vol. 69, No. 47, pp 11448-11449]. Dr. Curren suggested the EPA follow-up with organizations that have recently submitted *in vivo* acute systemic toxicity data and ask the submitters if they have used the recommended *in vitro* test procedures to estimate initial *in vivo* doses.

Dr. Curren asked if the OECD advisory document on the application of GLPs to *in vitro* toxicity testing is publicly available. Dr. Stokes said the OECD reports are typically not released until finalized at the OECD Joint Meeting (scheduled for November 2004), but he would inquire whether a final draft version could be made available. Dr. Curren did not necessarily agree that draft OECD TG 435 (*In Vitro* Membrane Barrier Test Method for Skin Corrosion) is the first test guideline to incorporate performance standards. He considered other OECD test guidelines, namely TG 432 (*In Vitro* 3T3 NRU Phototoxicity Test), TG 430 (*In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test), and TG 431 (*In Vitro* Skin Corrosion: Human Skin Model Test) to have what he considers basic performance standards. Dr. Stokes replied that the two *in vitro* skin corrosion methods adopted as test guidelines provide a list of 6 corrosives and 6 non-corrosives each, and state that a lab must be able to correctly identify all 12 substances with their version of the test method. ICCVAM considered this number suitable to demonstrate laboratory proficiency with the validated reference test method on which the test guidelines are based (e.g., EPISKIN™, EpiDerm™, Rat Skin TER). However, the ICCVAM does not feel the numbers are sufficient to adequately assess the validity of a new different version of a test method in order to demonstrate comparability with the validated method on which the guideline was based.

Dr. Stitzel inquired about the status of guidelines for the validation of computer methods. Dr. Stokes replied that ECVAM developed guidelines for QSAR and a summary of a 2002 ECVAM meeting on this topic was published in *Environmental Health Perspectives* as a mini-monograph (Volume 111, Number 10 August 2003). Dr. Halder, ECVAM, added that ECVAM is still working on this issue.

IV. ECVAM UPDATE²

Dr. Marlies Halder updated SACATM on ECVAM validation activities including: a) the ECVAM validation study of acute skin irritation, b) ECVAM activities on biologicals and ecotoxicology, c) six ECVAM workshops, and d) four consultation meetings. She began her presentation by summarizing recent ECVAM restructuring that has led to the creation of four key management “actions”:

1. *Action 1321 QSAR* [computational toxicology, QSAR(s)]
2. *Action 1322 Alternatives: Validation of alternative tests for the chemicals and cosmetics legislation* [topical toxicology, systemic toxicology, sensitization, carcinogenicity, and reproductive toxicology]
3. *Action 1323 Emerging: Validation for emerging areas, such as pharmaceuticals, biologicals, biomaterials and other products and enabling technologies* [GLP, Good Cell Culture Practice (GCCP), toxicokinetics, ecotoxicology, biologicals, and strategic developments]
4. *Action 1324 ECVAM Database Service on Alternative Methods* [databases and scientific information system]

A. Validation Study on *In Vitro* Methods for Acute Skin Irritation

The experimental component of the ECVAM validation study has two phases: phase 1 that ended in August 2004 and phase 2. In phase 1, the preliminary phase, the standard test protocols and prediction models were optimized and confirmed on 20 coded chemicals. Phase 2, the definitive phase, is occurring now and will evaluate the interlaboratory reproducibility and predictive ability

² Dr. Halder provided the names of ECVAM staff responsible for different activities in her presentation.

of the tests (3 labs per test with 60 coded chemicals). Phase 2 data analysis, publication and submission to the ECVAM Scientific Advisory Committee (ESAC) are expected to occur by April 2005. Dr. Halder presented a summary table of the phase 1 results for EPISKIN™, EpiDerm™, and SIFT test systems; they performed “very good,” “very good” and “good,” respectively. Interleukin 1 has recently been added as an endpoint and its inclusion appears to increase predictivity.

B. Biologicals and Ecotoxicology Activities

Dr. Halder defined biologicals as products that are produced by or derived from a living organism including vaccines, antitoxins, immunoglobulins, hormones, blood products, and poly- and monoclonal antibodies. This is a key area for ECVAM, because it involves a large number of animals, exposes the animals to high levels of distress, and alternative methods exists. ECVAM has published nine workshop reports on this topic in the journal *Alternatives to Laboratory Animals* and/or on the ECVAM web site (available at <http://ecvam.jrc.it>). Five workshops or meetings are planned for 2005.

1. Workshop on physico-chemical methods
2. Workshop on consistency of production approach
3. Follow-up of workshop 48: Replacement of the National Institutes of Health (NIH) Test for Rabies Vaccines [this is a joint activity with European Pharmacopoeia (Ph.Eur.), FDA, National Institute for Biological Standards and Control (NIBSC), and the World Health Organization (WHO)]
4. Expert meeting on alternatives in quality control of pertussis vaccines (in cooperation with Ph.Eur. and WHO)
5. Expert meeting on botulinum toxin (for therapeutical use)

ECVAM has finalized funding and management plans for 11 pre-validation and feasibility studies, four methods are accepted by Ph.Eur., and one validation study is planned for 2005 (serological methods for potency testing of whole-cellular pertussis vaccines). In 2003, ECVAM established a task force on biologicals whose members mainly work to identify promising alternative methods and provide comments on monographs, guidelines, and other regulatory issues.

Dr. Halder highlighted two specific validation efforts. The first, a validation study for six *in vitro* pyrogenicity methods, was finalized in 2003. Dossiers for the ESAC and ICCVAM peer review process are in preparation. This validation study includes a “catch-up” validation on whole blood and peripheral blood mononuclear cells (PBMC) using cryopreserved blood. She mentioned that an ECVAM/Directorate General for Health and Consumer Protection (DG SANCO) workshop is planned for January 2005 to identify and select alternative methods for validation related to shellfish toxin testing.

With respect to ecotoxicology, ECVAM published a workshop report in 2003 on the use of fish cell lines in acute toxicity testing and established a task force for ecotoxicology. In 2004, ECETOC and ECVAM held a workshop on three Rs approaches in this area. Three ongoing and planned projects are the: 1) evaluation of threshold approach (i.e., reduction in the number of fish used in acute toxicity testing), 2) optimization of cytotoxicity tests using fish cell lines, and 3) collaboration with the German authority on validation of the fish embryo test currently in the OECD testing guideline program.

C. Workshops³:

Dr. Halder summarized the goals, topics, participants, preliminary conclusions and recommendations from six recent ECVAM workshops:

1. *Metabolism: a Bottle-neck in In Vitro Toxicological Test Development (January 2004)*
2. *Dendritic Cells as a Tool for a Predictive Identification of Skin Sensitization Hazard - April 2004*
3. *Weight of Evidence Validation - May 2004*
4. *Chemical Effects on Mammalian Fertility - June 2004*
5. *Chronic Toxicity In Vitro: A New 3Rs Challenge - September 2004*
6. *QSAR Applicability Domain (AD) - September 2004*

D. Consultations Meetings

Dr. Halder briefly presented an overview of the goals, participants, outcomes and contact individuals for several consultation meetings.

1. *In vitro Micronucleus Test (MNT) - April 2004*
2. *Cell Transformation (CTA) - April 2004*
3. *Biokinetics - August 2004*
4. *Validation of QSAR for Estrogen Receptor (ER) and Androgen Receptor (AR) Binding - August 2004*

Dr. Halder concluded her presentation by announcing the imminent publication of two ECVAM workshop reports titled “Strategies to replace *in vivo* acute systemic toxicity testing” and “Validation principles for toxicogenomic-based tests.” Other workshop reports discussed are expected to be published in 2005.

E. SACATM Discussion

Dr. Stephens asked why the planned botulinum toxin workshop is limited to therapeutic use and does not appear to include the cosmetic use of botulinum in products such as BOTOX®. Dr. Halder responded that botulinum is defined as a pharmaceutical in Europe because it is injected into the skin rather than being applied dermally, thus BOTOX® in Europe is considered a pharmaceutical.

Dr. Curren asked about the status of the *in vitro* replacements for the rabbit pyrogenicity test that have gone through ECVAM validation. Dr. Halder responded that ECVAM is currently preparing background dossiers for peer review and is waiting for the “catch-up” validation studies to be finalized so that tests using cryopreserved blood can be included in the peer review. Dr. Halder said industry is likely using *in vitro* approaches to assess pyrogenicity, because Charles River Laboratory, Inc. sells one test method as a kit. Dr. Curren commended ECVAM on the quality of its workshops and asked if ECVAM would be taking a strong role in pursuing the implementation of workshop recommendations. He highlighted the skin sensitization workshop because of its importance in implementing the seventh amendment to the EU Cosmetics Directive⁴. Dr. Halder said ECVAM will be following up on the skin sensitization workshop recommendations and has already established a task force. Dr. Stitzel commended ICCVAM, NICEATM and ECVAM for their work since the last SACATM meeting.

³ Additional details about these workshops and consultations (including ECVAM contact staff) presented in Dr. Halder’s presentation are available at <http://ntp-server.niehs.nih.gov/ntpweb/index.cfm?objectid=652555EC-F1F6-975E-792DD9BEF9BE0190>

⁴ The seventh amendment to the Cosmetics Directive requires that by 2009 no further animal testing of cosmetics ingredients shall be conducted in the European Union for the purposes of the Cosmetics Directive regardless of the status of alternative, non-animal testing methods.

V. EVALUATION OF THE UNDER-PREDICTION RATE FOR THE *IN VIVO* RABBIT DERMAL IRRITATION TEST

This was a joint presentation by Dr. Stokes (Part I: Introduction) and Dr. Joseph Haseman (Part II Data Analysis).

A. Introduction

Dr. Stokes introduced the topic by providing a background of dermal irritation testing. The Draize rabbit skin test is an *in vivo* method used (with minor modification) since the 1940s to identify skin irritants or corrosives. However, the 2003 Globally Harmonized System of Classification and Labeling of Chemicals (GHS) encourages use of a tiered testing approach that incorporates valid and accepted *in vitro* techniques. ECVAM is currently validating three *in vitro* methods for assessing dermal irritation: EPISKIN™, EpiDerm™, and SIFT. Establishing “under-prediction”⁵ rates for the *in vivo* dermal irritation test will greatly enhance the evaluation of the usefulness and limitations of *in vitro* methods. Most importantly, the data will help determine acceptable false negative rates for irritant effects that an *in vitro* method would have to meet to be considered an acceptable replacement for the rabbit skin test.

Dr. Stokes next reviewed the current testing procedure used since 1981 (OECD TG 404) including a discussion of the test method protocol and dermal irritation scoring for erythema and edema. Prior to the early 1980s the test required 6 animals and now requires 1 to 3, a reduction that does not appear to compromise test outcome. He discussed how the erythema and edema scores are used to classify irritants, mild irritants and non-irritants in the GHS classification scheme. The test is sequential and classification is based on the mean scores of these measures. Overall, the erythema score impacts classification more than the edema score. In the current analysis, NICEATM used the GHS scheme to classify compounds because this will be the international standard in the next few years.

The only formal evaluation of the reproducibility of the rabbit dermal irritation test (i.e., Draize rabbit skin test) was conducted by Weil and Scala in 1971. Weil and Scala concluded that the test had moderate intra-laboratory and low inter-laboratory reproducibility. The low inter-laboratory reliability was primarily attributed to the subjective nature of the visual observations and differences in procedures between laboratories. However, this analysis has two major shortcomings that currently limit its use. First, the standard protocol used at the time of the analysis is different from the current Draize protocol used since 1981. Specifically, the studies described by Weil and Scala used a 24-hour exposure period versus the current maximum 4-hour exposure period. The longer exposure period could cause irritants to produce corrosive lesions. In addition, GLP guidelines were not in effect at the time of the Weil and Scala analysis.

NICEATM is using data from the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Skin Irritation and Corrosion Reference Chemicals Data Bank to estimate the likelihood of under-predicting: 1) an irritant as a mild irritant, 2) an irritant as a non-irritant, and 3) a mild irritant as a non-irritant. A wide-range of chemical classes is represented in the NICEATM analysis (164 chemicals from 197 studies) and all studies were performed according to OECD TG 404 and GLP. Most chemicals were tested in 3 to 6 animals (mostly 3 or 4) and 23 were tested in multiple studies. NICEATM continues to expand its database by incorporating high quality data received in response to a request issued in a July 16, 2004 Federal Register notice (Vol. 68, No 136, pp 42066-42067) and by reviewing dermal test reports in the EPA

⁵ In this presentation under-prediction refers to a comparison of rabbit data with rabbit results and not rabbit results with human data.

TSCATS database. However, many reports in the EPA TSCATS database are not amenable to analysis, because they do not provide individual animal data and/or purity information. The NICEATM analysis will be repeated when a sufficient amount of new data is identified.

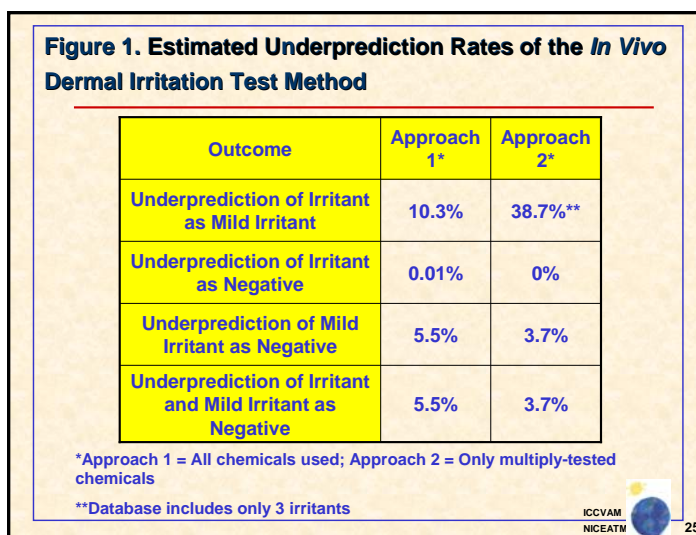
B. Data Analysis

Dr. Haseman, a consultant formerly with the NIEHS, began his presentation by defining under-prediction rate as the “probability that an irritant substance will not be classified as an irritant when subjected to the test”. The under-prediction rate depends on two factors: 1) the distribution of animal responses for substances assigned to a specific classification category and 2) the strategy used to assign a test substance to a classification scheme.

To calculate under-prediction, Dr. Haseman first determined the distribution of animal responses for each irritancy class (irritant, mild irritant and non-irritant). He then used this distribution and possible outcomes determined by

erythema and edema scores in three animals to calculate response probabilities for a specific irritancy classification (assumed to be representative). For each irritancy classification, the probabilities were summed to provide overall classification likelihoods. He performed this analysis using two approaches: 1) “approach 1” where all substances in the database were used or 2) “approach 2” that only used substances tested multiple times. Although approach 1 will allow for inclusion of a greater number of substances, it

will not capture between test variability. This may result in a slight underestimate of the under-prediction rate. On the other hand, approach 2 may not be as reliable because it allowed for inclusion of only 23 substances (8 non-irritants, 12 mild irritants and 3 irritants). Dr. Haseman believes approach 2 may overestimate the under-prediction rate estimates, because it is biased to include substances prone to produce ambiguous scores, hence the reason for testing them multiple times. Dr. Haseman presented several slides illustrating calculations used for approaches 1 and 2. His summary slide of estimated under-prediction rates for both approaches is presented in Figure 1. Dr. Haseman noted the under-prediction rate estimates for an irritant to be falsely classified as a mild-irritant is between 10.3% (approach 1) and 38.7% (approach 2), and likely closer to 10.3%. Other under-prediction scenarios show that it is relatively unlikely that an irritant or mild irritant will be wrongly classified as a non-irritant. Dr. Haseman also presented the mean scores for the 3 irritants tested multiple times. Unlike other substances in the database where erythema scores appear to most important in determining classification, the edema score appears to be driving the scoring for these three multiply tested irritants. Based on erythema score alone, all of these substances would be classified as mild-irritants rather than irritants. He also noted what appeared to be poor inter-laboratory reproducibility of classification based on the edema response that may be attributed to the more subjective nature of edema scoring



C. Public Comment

Sadhana Dhruvakumar, People for the Ethical Treatment of Animals (PETA), had two comments. First, she believes a comparison of rabbit data to rabbit data, like that presented in the analysis,

produces measures of reproducibility and repeatability and not under-prediction. PETA would like ICCVAM-NICEATM to compare the rabbit data to human data and use this as the gold standard against which proposed *in vitro* replacement assays are judged. She recognizes the difficulties involved with obtaining human data, but feels in this case that human data for dermal irritation are available in the form of clinical data from human skin patch testing. Second, she is glad to see Corrositex® moving forward as an OECD test guideline, but is concerned that the draft test guideline only recommends its use as part of a tiered testing strategy (where a negative result would be subject to confirmatory test in animals) even though a 1999 ICCVAM-organized peer-review panel found Corrositex® “useful as a stand alone assay for evaluating the corrosivity or non-corrosivity of acids, bases, and acid derivatives.” This conclusion is not referenced in the draft OECD test guideline. The ICCVAM report also says that any cost-savings or convenience of Corrositex® as part of a tiered strategy would be lost. She asked for the scientific rationale for deviating from the 1999 conclusions in the OECD test guideline.

D. SACATM Discussion

Although Dr. Stitzel thought the analysis was very useful, she believes use of the term “under-prediction” is misleading, because it implies a comparison between rabbit results and human data. She suggested that the analysis clearly state the comparison is one of rabbit data with rabbit results. Dr. Flournoy agreed with this point and felt the analysis is very thoughtful, although she thought it is best characterized as an evaluation of internal reproducibility. Dr. Flournoy did not believe there is a need to conduct more animal tests to further the analysis. She believes any resources directed towards the analysis should focus on examining likely future models rather than the historical model. For example, the existing data could be analyzed in a number of ways to evaluate new testing schemes. Specifically, calculated probabilities could be used to predict how other testing strategies may perform (e.g., the effects of performing a sequential test procedure or the impacts of a hazard categorization rule change).

Dr. Monteiro-Riviere also agreed that the term “under-prediction” implies a comparison to human exposure scenarios. In addition, she questioned whether the rabbit is a suitable dermal toxicity model for the human given that rabbit skin is very thin and blood flow is very high, which could result in greater absorption compared to human skin and potential over-prediction of human response. She also questioned whether a 4-hour exposure period is sufficient. She asked Dr. Haseman for clarification on whether the data on repetitive applications are based on the same or different animals. Dr. Haseman said the data refers to different animals tested in the same laboratory with the same concentration. Dr. Haseman agreed that, ideally, sufficient human data would exist to allow an independent classification of the chemicals as irritants that was not linked to the same test being evaluated. His understanding is that there are not enough human data to allow such an analysis. Dr. Monteiro-Riviere was concerned about the use of mean response to categorize a chemical. Dr. Haseman said an alternative classification strategy could be to categorize a chemical based on the highest responding animal and such an approach would guarantee no under-prediction in the current analysis. Dr. Stokes reiterated that the classification scheme used by NICEATM is the GHS international standard. Dr. Stokes believes it would be appropriate to revisit the global guidelines at some point in the future.

Dr. Smith complemented Dr. Haseman on his analysis. She thought the two key conclusions are: 1) the likelihood that an irritant would be misclassified as a non-irritant is less than 0.01% and 2) additional animal and human studies are not needed to evaluate the predictability of the animal models. Dr. Sonnenschein asked for an explanation of what parts of the rabbit are used for testing and why. Dr. Stokes said the dorsum of the rabbit on either side of the dorsal midline is used. Dr. Sonnenschein asked whether the rabbit ear is ever used in dermal irritation studies. Dr. Monteiro-Riviere said the skin on the back of the rabbit is comparable to the human forearm and

that the rabbit ear is generally not considered a suitable model. Dr. Stokes emphasized the need for more human data to evaluate the *in vivo* models.

Dr. Curren commented that human data are available for several of the chemicals evaluated in the ECVAM pre-validation and phase I studies on *in vitro* methods for acute skin irritation. He believes the human data differ from the rabbit data in the direction of showing less irritation. Dr. Curren was also concerned about use of the term “under-prediction” for the reasons mentioned above, and also because he believes the results represent *minimum* under-prediction rates, because inter-laboratory variability is not adequately represented in the analyses. He suggested including more than three irritant categories in the analysis to reflect the reality that the degree of irritation caused by a chemical is a continuum. Dr. Curren believes more data might be submitted to NICEATM if stakeholders with data are provided an opportunity to comment during the evaluation period rather than after NICEATM has completed its analyses.

With respect to the utility of existing human data, Dr. Portier said although this data may be available, it is likely biased towards milder irritants. Thus, positive predictivity for a severe irritant may be difficult to evaluate and the human data may be most suitable to estimate the over-sensitivity of the animal model. The primary purpose of the NICEAM analysis is to provide information on the chances that a chemical can vary between classes just based upon the rabbit data. In turn, this information can be used to help evaluate potential alternative *in vitro* tests. Dr. Portier also commented that this analysis is a preliminary evaluation, so comments and suggestions can be incorporated into future analyses. In addition, he said the NTP is committed to making the database available online.

VI. PRELIMINARY EVALUATION OF THE UNDER-PREDICTION RATE FOR THE *IN VIVO* RABBIT OCULAR IRRITATION TEST

This was a joint presentation by Dr. Stokes (Part I: Introduction) and Dr. Joseph Haseman (Part II Data Analysis).

A. Introduction

The Draize eye irritation test method has been used since the 1940s to detect eye irritation and serious eye damage. Dr. Stokes presented the 2003 GHS tiered-testing approach for eye irritation, which like the GHS dermal irritation approach, states that valid and accepted *in vitro* methods should be considered for classifying and labeling chemicals for potential irreversible eye effects. Numerous non-animal methods have been developed since the 1980s. ICCVAM is currently evaluating four methods for evaluating severe or irreversible ocular irritants and corrosives: 1) ICE, 2) IRE, 3) BCOP, and 4) HETCAM. The purpose of the NICEATM under-prediction analysis is to evaluate the likelihood of under-predicting⁶ an ocular corrosive or severely irritating substance as a nonsevere irritant/nonirritant using the Draize rabbit eye test and the 2003 GHS classification scheme. This analysis may assist in establishing false negative rates that *in vitro* test methods may need to achieve to be considered a complete replacement for the current rabbit eye test.

Dr. Stokes next reviewed the specifics of the test protocol for assessing eye irritation. The test is sequential and classification is based on the mean scores used to evaluate the iris, conjunctiva and degree of corneal opacity. In addition, he summarized the current GHS irritancy classification scheme for category 1 irritants (irreversible effects on the eye/serious damage), category 2A

⁶ In this presentation under-prediction refers to a comparison of rabbit data with rabbit results, and not rabbit results with human data.

irritants (irritating to the eyes), category 2B irritants (mildly irritating to the eyes) and non-irritants.

The reproducibility of the Draize rabbit eye test using the Federal Hazardous Substances Act (FHSA) classification system was evaluated by Weil and Scala in 1971. They concluded that the test had moderate intra-laboratory reproducibility and low inter-laboratory reproducibility. The low inter-laboratory reliability was attributed to the subjective nature of visual observations used in the test. However, the Weil and Scala analysis is limited for current use for two main reasons. First, GLP Guidelines were not established at the time of the analysis. In addition, it is not possible to apply current GHS, EPA or EU classification data to the data analyzed by Weil and Scala, because individual animal data are not available.

NICEATM developed an *in vivo* ocular database based on 505 studies of 448 substances (79 formulations and 369 chemicals), although many of the substances are commercial products with unknown formulations and chemical composition. NICEATM conducted two preliminary analyses. The first one only involved the ECETOC database (“ECETOC database”) and the second included this database plus additional data submitted to NICEATM in response to a March 2004 Federal Register notice⁷ (“Total database”). NICEATM will continue to update its overall under-prediction estimate as new information is added to the database. In addition, NICEATM will also evaluate inter-laboratory performance for substances tested in multiple laboratories and estimate relative under-prediction rates for each GHS decision criteria used for classification (i.e., severity, persistence, severity and persistence, and tissue type).

B. Data Analysis

Overall, Dr. Haseman said the approach used to estimate under-prediction rates for *in vivo* ocular irritancy is similar to those described for dermal irritancy, although the ocular strategy is more complicated. Dr. Haseman emphasized that the under-prediction rate depends on two factors: 1) the distribution of animal responses for substances assigned to a specific classification category (1, 2a, 2b, or non-irritant) and 2) the strategy used to assign a test substance to a classification scheme. In the current presentation, Dr. Haseman is only going to present under-prediction estimates for category 1 irritants classified as 2a, 2b or non-irritants. One complication in the ocular analysis is that several substances tested at multiple concentrations showed concentration inversion, such that a mid-concentration produced an irritation response and a higher dose produced a less irritating response. In these cases, Dr. Haseman assumed that the highest irritation response is “true” and lesser irritation effects at higher concentrations are “false negatives.” If there are biological explanations for the dose inversions, then classifying the higher concentration effects as “false negatives” would increase the under-prediction estimates.

⁷ Data were received by Access Business Group; Cosmetic, Toiletry, and Fragrance Association (CTFA); ECETOC; FDA; the European Diisocyanate and Polyol Producers Association (ISOPA); EPA TSCATS; and the Japanese National Institute of Health Sciences.

The responses for individual chemicals within a category are much more heterogeneous for ocular irritants than for dermal irritants (i.e., they have different response profiles within a category). For this reason, Dr. Haseman performed this analysis using two assumptions. For “Assumption 1,” responses are assumed to be homogeneous within a given category (i.e., it is assumed that animals have the same pattern of response for all chemicals within a given category). This approach requires only one calculation, but may underestimate the under-prediction rate if the data are in fact heterogeneous. The “Assumption 2” approach assumes responses are heterogeneous within a category (i.e., all animals have a different pattern of response for all chemicals within a given classification category). This approach will lead to higher misclassification rates than Assumption 1, but may overestimate the under-prediction rate. Dr. Haseman believes the true under-prediction rate is between Assumptions 1 and 2, and likely closer to Assumption 2. Much of the heterogeneity for category 1 irritants is due to a relatively high percent of lesser responding animals tested for a particular compound.

Figure 2. Estimated Underprediction Rate

GHS Classification Underprediction	ECETOC Database		Total Database	
	Assumption 1	Assumption 2	Assumption 1	Assumption 2
as Category 2A	7.77%	9.03%	3.71%	6.55%
as Category 2B	4.38%	10.8%	2.77%	8.59%
as Nonirritant	0.02%	0.4%	0.22%	2.26%
as Undetermined	0.30%	0%	0.37%	0.07%
Total	12.47%	20.23%	7.07%	17.47%

ICCVAM
NICEATM 30

Dr. Haseman’s summary slide of estimated under-prediction rates for both approaches is presented in Figure 2. Notably, a category 1 irritant is seldom under-predicted as a non-irritant (0.02 to 2.26%). More likely, a category 1 irritant is under-predicted as a 2a or 2b irritant (2.77 to 10.8%). Although the total under-prediction rates for a category 1 substance range from 7.1% to 20.23% for the GHS classification scheme, Dr. Haseman believes the rate is likely between 15 to 18% (between Assumption 1 and 2, but closer to Assumption 2). However, if concentration inversions are biologically plausible, then under-prediction rates would decrease by 3 or 4%.

C. Public Comment

Dr. Dan Marsman, Proctor and Gamble, said the dermal and ocular analyses are very useful. He suggested NICEATM assess the correlation between the corneal opacity score and the other scores (for iris and conjunctiva) for severe irritants. Although this would be a departure from the GHS classification scheme, he believes this would better reflect the human condition where corneal effects tend to account for severe eye irritation. Importantly, the ocular *in vitro* assays tend to focus on the corneal response, which he considers the most important determinant of irreversible, ocular toxicity potential. Dr. Sonnenshein asked why the isolated corneal response is considered most important. Dr. Marsman replied that he is not aware of cases where irreversible eye effects are observed in the absence of corneal damage.

Sadhana Dhruvakumar, PETA, said the analyses are very informative as measures of reproducibility and could be useful to compare the reproducibility of the *in vivo* and *in vitro* tests. However, she questioned the ultimate utility of attempting to draw “under-” or “over-prediction” conclusions given the limitations in obtaining human data. Dr. Stevens suggested that NICEATM-ICCVAM consider exploratory efforts to contract out the work of gathering human data, because this information is unlikely to be submitted via traditional data solicitations.

Dr. Jim Sherman, BASF, also cautioned against use of the term “under-prediction” and thought “variability” would be a more apt description of the dermal and ocular analyses. He also discussed the difficulties of responding to changing testing schemes and labeling requirements and encouraged ICCVAM to think about a globally harmonized system that lets test be useful for long periods of time.

D. SACATM Discussion

Overall, Dr. Curren said the lead discussants (Drs. Curren, Theran, Flouroy) are very appreciative of the analyses. Understanding the variability inherent in the animal test is very important and useful for later *in vitro* comparison and validation. He thinks additional steps need to be taken to assess what is “true” or “not true” *in vitro* tests including understanding the comparability of mechanisms in the *in vitro* and *in vivo* tests. Dr. Curren said like the dermal irritation analysis, the results should be viewed somewhat cautiously, since they are based on what is happening in a single laboratory, so he considers these to be minimum under-prediction estimates.

Dr. Flornoy said that many of her comments from the previous study also apply here, but she had a couple of additional points. First, she wondered whether a log-linear model could be used to provide estimates of variances associated with the misclassifications. Second, she thought interval censoring techniques could be used to include studies that are now being excluded, because the study did not extend for 21 days.

Dr. Theran was pleased with NICEATM’s efforts and he felt the results show that the animal test should not necessarily be considered the gold standard. He asked how NICEATM anticipates using the data. He is concerned that the under-prediction numbers will stand as the accuracy of the animal test and not be recognized as a minimum under-prediction estimate given that inter-laboratory variability is not incorporated. Dr. Stokes was not sure exactly how the analysis would be used in the future, but said the results of the under-prediction analyses would be supplied to regulatory agencies as they make decisions about whether to accept a particular *in vitro* method. Further, the data reflect tests conducted in a large number of laboratories and thus inter-laboratory factors are built into the analysis to some degree. In terms of accuracy (i.e., how well does the rabbit test predict human response), NICEATM is trying to determine whether there are cases where the chemical caused permanent eye injury in the human that did not occur in the rabbit. Dr. Portier noted that NICEATM analyses can be used to evaluate whether the variability of an *in vitro* assay matches the variability seen in the *in vivo* assays. Failure of an *in vitro* assay to meet the *in vivo* guideline does not necessarily mean the *in vitro* assay would be rejected, but provides a degree of confidence that helps the scientific evaluation process.

Dr. Haseman recognized the circularity of the analysis in that the accuracy of the classifications is not evaluated independently, which may result in bias toward a lower under-prediction estimate. He does not consider the estimates to represent reproducibility, because that would require a range of chemicals tested 2 or 3 times. The chemicals tested multiple times in the current analysis are not a random sample and are biased towards variability, thus it would be inappropriate to focus too much on them. Dr. Willhite suggested analyzing the extent to which variability can be attributed to a particular chemical class. There may be some types of chemicals that produce a more uniform response and others that produce a more variable response. Dr. Goldberg felt *in vitro* assays would not be used, if they display the type of variability demonstrated for the Draize eye test. He cautioned about accepting a low under-predictability rate, such as 1%, because it translates to a significant number of under-predictions when the number of chemicals to be tested is considered.

VII. ICCVAM NOMINATIONS

Dr. Stokes discussed the two major current ICCVAM nomination activities: 1) ocular and dermal toxicity test methods/approaches for antimicrobial cleaning products and 2) an update on *in vitro* endocrine disruptor test methods

A. Ocular and Dermal Toxicity Test Methods and Approaches for Antimicrobial Cleaning Products

On June 21, 2004, ICCVAM received a letter from the Director of the EPA Office of Pesticide Programs (OPP) stating that OPP and the Pesticide Program Dialogue Committee (PPDC) are working together to develop a non-animal approach for assessing skin and eye irritation potential for antimicrobial cleaning product formulations. As part of this activity, OPP is planning a technical workshop to evaluate this approach under the auspices of the PPDC. OPP has asked ICCVAM to conduct a formal technical review of the approach.

ICCVAM has discussed the request and has four recommendations for ICCVAM involvement:

1. ICCVAM considers this issue a high priority, because the products and ingredients are applicable to several ICCVAM agencies and are consistent with the EPA nomination of non-animal test methods for ocular irritancy and corrosion in 2003.
2. ICCVAM recommends that the most appropriate approach to evaluate this approach is to convene an ICCVAM-coordinated independent, scientific expert panel with the opportunity for public comment.
3. ICCVAM recommends that the PPDC, NICEATM, and the ICCVAM Ocular/Dermal Working Groups coordinate activities.
4. ICCVAM recommends that an expert panel meeting take place in the fall of 2005 or approximately six months following receipt of a complete submission package. The expert panel report would then be released for public comment, presented to the EPA Science Advisory Board, and ICCVAM would forward final recommendations to federal agencies. EPA would then consider those recommendations in determining acceptability of the non-animal approaches.

B. *In Vitro* Endocrine Disruptor (ED) Test Methods Update

Dr. Stokes provided SACATM with an update on two endocrine disruptor test method nominations:

1. A biosensor system that can assess estrogen receptor binding and transcriptional activation (IA, Inc.)
2. Stably transfected recombinant cell-based estrogen receptor (ER) transcriptional method (LUMI-CELL™) (XDS, Inc.).

Both of these methods fit ICCVAM preference guidelines, because they do not require the use of animals or tissue for the receptor source and do not use radioactive methods. ICCVAM also suggests establishing performance standards for ER binding, androgen receptor (AR) binding, ER transcriptional activation (TA) and AR transcriptional activation. Following receipt of the above test method nominations, NICEATM published a Federal Register notice requesting comment on these test methods and requesting additional nominations of *in vitro* ED test methods that adhere to guidelines presented 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). No comments were received on the IA, Inc. and XDS, Inc. nominations and NICEATM received notices of intent to nominate and/or preliminary data for three other test methods:

1. CertiChem, Inc. – MCF-7 cell proliferation assay (letter of intent and draft submission for comment).

Minutes from the October 2004 SACATM Meeting

2. Institute for Risk Assessment Sciences (IRAS), the Netherlands – H295R cell line aromatase screening assay (letter of intent and preliminary submission).
3. U.S. EPA – Dr. Earl Gray indicated intent to submit ER binding/TA assays for consideration (nothing received to date).

NICEATM is currently reviewing the recent submissions and the ICCVAM ED working group has developed five draft recommendations on the XDS, Inc. LUMI-CELL™ ER test methods, because this is the only method for which standardized protocols and data were received:

1. LUMI-CELL™ should be given high priority for validation study to evaluate chemicals for potential ER agonist and antagonist studies.
2. Independent standardization and a three-phase validation study conducted in at least three laboratories should be conducted. Progression from one phase to the next would be dependent upon successful completion of the previous phase.
3. NICEATM should coordinate the validation studies with the European and Japanese Centers for the Validation of Alternative Methods (ECVAM and JCVAM/NIHS, respectively). Ideally, the validation study would involve one laboratory in each of the three geographic regions (United States, Europe and Japan).
4. XDS should conduct additional ER antagonist studies to optimize the LUMI-CELL™ assay, because only a small number have been evaluated to date.
5. Following the validation studies, ICCVAM should develop and propose performance standards for the ER TA assays, conduct a technical evaluation of the validation studies (including an independent peer-review), and develop and disseminate the ICCVAM test recommendations to federal agencies.

ICCVAM will consider SACATM's comments as it releases final recommendations on the nominations and NICEATM will request funding for the recommended studies from the Director, Environmental Toxicology Program, NIEHS.

C. Public Comment

Dr. George Clark, XDS, Inc., thanked Dr. Stokes for his presentation and asked if there was any follow-up on the comment made by Dr. Dean at the last meeting that ICCVAM agencies should bear some responsibility for sponsoring their validation studies that support technology transfer.

Citing the Departments of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriations Bill for 2005, Sara Amundson (Doris Day League) noted a specific call by the Senate Appropriations Committee for EPA money to be set aside for validation studies of non-animal and alternative methods that may not be considered 'computational toxicology' methods.

Dr. Becker asked how the approach presented by Dr. Stokes for the ED nomination addresses the concern raised in the expert review on the use of systems having patent restrictions.

D. SACATM Discussion

Ocular and Dermal Toxicity Test Methods and Approaches for Antimicrobial Cleaning Products
Dr. Smith wondered why anti-microbial agents are singled out in the EPA request. Dr. Stokes said the companies initiating this effort believe they have a sufficient amount of data to substantiate the validity of non-animal approaches for dermal and ocular toxicity for anti-microbial products. EPA is the only regulatory agency that requires the submission of data for this product category. Dr. Stokes said the approach proposed by these companies includes several *in vitro* methods and human testing for dermal irritation. Dr. Curren elaborated on the issue, because his company, the Institute for In Vitro Sciences, is working with the companies

Minutes from the October 2004 SACATM Meeting

who initiated this effort. The companies are pursuing the nomination, because they claim to have considerable, positive experience in using non-animal methods to determine appropriate hazard classifications for EPA warning labels for antimicrobial cleaning products. Thus, this is a situation where there is a fairly well defined category of material whose formulations are reasonably well-known and for which a significant amount of *in vitro* and *in vivo* data exist. Further, ICCVAM will consider *in vitro* test methods proposed for a specific range of compounds. Dr. Goldberg asked what specific tests are being considered. Dr. Curren responded that data collection is just beginning, but it's assumed that most of the *in vitro* ocular data will be derived from the bovine cornea assay, the cytosensor, and a 3-dimensional human ocular model. A 3-dimensional human skin model will be used to describe dermal toxicity, but the majority of skin irritation information would come from human clinical studies.

Dr. Hayes is concerned that SACATM is being asked to make a recommendation in the absence of any data. In addition, it is also his understanding that priority will be given to tests that apply to multiple agencies rather than one subset within a single agency. He questioned why the anti-microbial nomination received such a high rating despite ICCVAM not having seen the specifics of the approach. Dr. Stokes responded that the high priority rating is determined by two factors. First, the materials are not unique to EPA, but EPA is the only agency that requires submission of data for compounds that have an anti-microbial claim. The Consumer Product Safety Commission (CPSC) has regulatory oversight of these agents as cleaning products, but does not require the submission of data. Dr. Wind commented that CPSC requires that the agent be appropriately labeled, but does not require the use of animal data to support the label claim. Anti-microbials are also relevant to the FDA such as for surgical scrubs and medical device disinfection. The other reason ICCVAM gave the nomination a high priority is because this is the first time an entirely non-animal approach is being proposed. The findings of the expert panel on ocular and dermal toxicity test methods and approaches for antimicrobial cleaning products could be extended to other products or chemical classes and act as a prototype. In addition, the approach will likely be evaluated by EPA regardless of ICCVAM's participation.

Dr. Sonnenschein asked who would evaluate the data. Dr. Stokes replied that the data and approach will be organized by industry according to ICCVAM submission guidelines. Once ICCVAM determines the completeness of the submission, NICEATM in collaboration with the ICCVAM will convene an independent expert panel. The expert panel will prepare a report that is provided to the ICCVAM and forms the basis for the recommendations ICCVAM makes to agencies. ICCVAM believes it is a high priority to proceed as outlined, but further review will not occur unless the submission package is complete. Dr. Hayes asked if the review process could be conducted in such a way that it would also apply to other non-antimicrobial cleaning products. Dr. Stokes said this issue has been raised to the submitters and their response was that they feel confident about the test methods when applied to a broader range of compounds, but there is a need to substantiate the antimicrobial claim. Dr. Smith asked if an additional ICCVAM review would be required if others were to say that this approach applies to other products or would performance standards be developed. Dr. Stokes appreciated the suggestion and said the ICCVAM intends to have performance standards for every new test method or approach it considers.

Dr. Stitzel asked whether any member of SACATM thought ICCVAM should not move forward on this nomination. All SACATM members supported ICCVAM moving forward with this nomination. Dr. Sonnenschein asked whether SACATM would be able to reconsider its recommendations when presented with additional data and suggested the nomination be presented to SACATM when the complete submission package is received. Dr. Portier asked Dr. Stokes to explain why more background information outlining how ICCVAM and NICEATM reached its

Minutes from the October 2004 SACATM Meeting

recommendations was not made available to SACATM. Dr. Stokes reviewed the published ICCVAM nomination criteria and process and said in this process, ICCVAM formulates preliminary recommendations and then seeks SACATM's advice before making final recommendations. In this case, the nomination is for review of a test method approach for which a test method submission has not yet been prepared. ICCVAM is asking SACATM to comment on whether ICCVAM should commit time and effort to this nomination. Dr. Portier commented that SACATM only has the letter from EPA in its background material notebook and asked Dr. Stokes if there is any additional information. Dr. Stokes responded that ICCVAM learned more about the nomination at a recent meeting with EPA and industry representatives; SACATM has all available information on the nomination. Dr. Merenda added that ICCVAM is receptive to the nomination, because the EPA previously nominated *in vitro* methods for assessing ocular effects as a priority. He noted that ocular methods were given a high priority by both ICCVAM and SACATM. In addition, ICCVAM believes it important that ICCVAM and the EPA pesticide program not duplicate efforts on ocular toxicity.

Dr. Wind said EPA is moving ahead on this issue regardless of ICCVAM's participation. The initial proposal had the approach discussed by the EPA Science Advisory Panel prior to ICCVAM's review. ICCVAM did not feel it appropriate to have a federal agency pursuing an activity that is under its purview. She understood the lack of data is problematic, but believed pursuing the activity under the auspices of ICCVAM is most appropriate. Dr. Stitzel thought it is sensible to avoid a scenario where an agency works around ICCVAM, potentially resulting in the formulation of conclusions on alternative methods by a science advisory panel that ICCVAM could not support. Dr. Goldberg agreed, but was concerned that a bottle-neck might be created if every assay requires an ICCVAM discussion at the earliest stages. He said the nomination is consistent with early recommendations by the Johns Hopkins Center for Alternatives to Animal Testing (CAAT) Board that advocate a modular approach to validation where a method is first assessed on a single group of chemicals. Although Dr. Goldberg thought the nomination should proceed, he was concerned about the lack of information provided to SACATM and the appearance that ICCVAM is monitoring government agencies' activities. He believed strong communication may help alleviate the conflict.

In Vitro Endocrine Disruptor (ED) Test Methods Update

Dr. Portier asked to what degree the XDS nomination package and evaluation could be made available to SACATM and the public since NICEATM has reviewed the preliminary data. Dr. Stokes replied that NICEATM looked at the nomination package to see if the essential test method components recommended by ICCVAM for an ER TA assay are met. He believes the protocol could be made available⁸. In addition, NICEATM looked at data for some of the reference chemicals and feels the data warrant a phased validation study. The intent is not to have a formal review of the preliminary data, but to ask whether the preliminary data substantiates a move into phase I validation to see if the results are reproducible in multiple laboratories. If not, the nomination will not proceed. Dr. Hayes suggested ICCVAM present an overview of the ICCVAM nomination process with a description of how the nomination fulfilled each step. Dr. Portier asked ICCVAM and NICEATM to make the nomination package available to SACATM for future nominations. Dr. Willhite did not have an objection to proceeding with the nomination, but asked how the results from an ER TA assay would be used in the regulatory scheme. Dr. Stokes said the ER TA assay would provide mechanistic data that could be considered in a weight of evidence decision on the outcome of testing from a Tier 1 ED screening

⁸ The test method protocol is publicly available and was published in NIH Publication No. 03-4505: Background Review Document: Current Status of Test Methods for Detecting Endocrine Disruptors: *In Vitro* Estrogen Receptor Transcriptional Activation Assays, October, 2002

battery. The weight of evidence decision would determine if additional multi-generational testing should be conducted. Dr. Stokes added that ECVAM selected 11 ED methods for a multi-laboratory, pre-validation study and the XDS method would be incorporated into the pre-validation study as a first phase. There is no intention to move any of the 11 methods through later phases if they are not promising in the pre-validation studies.

Dr. Stitzel asked if any member of SACATM thought that ICCVAM should not move forward on this nomination. All SACATM members supported ICCVAM pursuing the ED nomination.

VIII. TOXICOLOGY IN THE 21ST CENTURY: A ROAD MAP FOR THE NATIONAL TOXICOLOGY PROGRAM

Dr. Portier summarized recent progress on the NTP Vision for the 21st Century *to support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations*. He primarily focused on the development of a document titled “A National Toxicology Program for the 21st Century: A Roadmap to Achieve the NTP Vision” (“NTP Roadmap”). He invited SACATM to comment on the document, although he said NTP does not foresee substantive changes to it.

The NTP is a multi-agency program that helps address data needs of regulatory agencies as they make public health decisions. Dr. Portier presented a list of the federal agencies that routinely participate in NTP activities. The list included the eight agencies represented on the NTP Executive Committee that provides advice on NTP research priorities. He reviewed the functional organization of the NTP, the primary activities of laboratories, centers and offices contributing to the NTP, and the NTP’s historical testing strategy. Currently, the NTP has an agent-specific testing program, although over the past 7-10 years it has funded a considerable amount of mechanism-based research aimed at identifying how chemicals cause toxicity. The overall goal of the NTP Roadmap is to outline an approach where mechanistic information is used to improve the process by which NTP generates information for making public health decisions. In general terms, the NTP seeks to improve and update its animal bioassays, incorporate mechanism-based information into a screening program to help set testing priorities, and establish a database to allow future validation of the mechanistic data.

A. Roadmap Retreat

Dr. Portier summarized the NTP retreat held in August 2004. Retreat attendees were separated into four breakout groups and asked to clarify the wording of the draft NTP Roadmap document and suggest activities and priorities for roadmap for the next 5 to 10 years. The four breakout groups were: 1) High-Throughput Screening, 2) Bioassay Review and Redesign Activity Matrix, 3) Medium-Throughput Screening and ‘Omics’, and 4) Data Analysis and Interpretation. Dr. Portier identified retreat attendees and the proposed activities/priorities for the roadmap. Dr. Portier said NTP intends to test a fixed set of ~ 1000 to 2000 compounds in all the mechanistic studies. This set would include both compounds that NTP has already studied and additional compounds not tested by the NTP. He invited nominations of chemicals to include in a high-throughput screening process for the program. Dr. Portier explained that medium-throughput screening refers to the use of non-rodent whole animal assays, such as zebrafish and non-vertebrates. Medium-throughput models may have considerable use in minimizing the use of mammalian vertebrate systems. ‘Omics’ includes cell-based assays and *in vitro* measurements of gene expression.

Minutes from the October 2004 SACATM Meeting

With respect to bioassay design, Dr. Portier noted that some of the activities identified by the Bioassay Review and Redesign breakout group are already being implemented. For example, the NTP has been working to make its databases more useful and also working with other potentially large producers of toxicity data, such as the Korean National Toxicology Program and the Ramazzini Foundation, to enhance their databases. The NTP intends to sponsor a series of future workshops to look at issues related to the bioassay's redesign.

The most critical issue for the NTP Vision is to determine how mechanistic information could be used to make public health decisions. Currently, most mechanistic information has been used to address hazard characterization, typically to qualify what was already observed *in vivo*. The question now is how to use these techniques to answer questions about hazard in the absence of animal studies or to enhance and clarify findings observed in animal studies. More difficult will be determining how to use these techniques to quantify risk (i.e., to determine risk per unit of exposure). NTP has developed a plan to address these issues that will require establishing a database populated with information for a large set of chemicals and assays. NTP plans to convene workshops to aid interpretation of the database analyses. The NTP Board of Scientific Counselors, SACATM, ICCVAM and other agency representatives will be kept informed of roadmap activities. NTP will utilize the ICCVAM validation process if it identifies a method(s) that leads to reducing, refining, or replacing the use of animals in testing. In addition, ICCVAM will be kept informed of NTP's Roadmap activities to ensure the data for promising methods are organized in such a way that when a method(s) is presented to ICCVAM it will be ready for pre-validation, if not for full validation studies.

B. Public Comment

Sara Amundson, Doris Day Animal League, thanked Dr. Portier for his presentation. She supports NTP's efforts to maximize public participation in this process and the inclusion of specific timelines in the NTP Roadmap. She had two recommendations for the NTP Roadmap document. First, she suggested the NTP modify the second bullet at the beginning of the document to state "develop and validate improved testing methods, and where feasible, ensuring that they reduce, refine, or replace animals." With respect to NTP collaborations with other agencies, she noted EPA's Computational Toxicology Program is fully funded for over 13 million dollars for fiscal year 2005. Additional language in the Departments of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriations Bill for 2005 states that other promising alternative methods should be subject to EPA money for validation studies. She was very disturbed at the March 2004 SACATM meeting to hear that EPA had research and development money, but not validation money for endocrine screening methods. Ms. Amundson also noted that the U.S. House of Representatives' version of the 2005 appropriations bill mentioned above commends the activities of ICCVAM and recommends NIEHS improve its monetary commitment to ICCVAM.

With respect to the NTP Roadmap's referencing additional scientific outreach and communication, she noted that a California statute requires the use of scientifically validated, federally approved alternatives. However, she does not believe this statute is widely known. She suggested ICCVAM, NIEHS, and the California Environmental Protection Agency or other California agency co-sponsor a workshop for industry to teach methodology and encourage utilization of alternative methods.

Ms. Amundson was disappointed that the Federal Register notice announcing the availability of protocols for the updated, standardized, *in vitro* cytotoxicity test method for estimating acute oral

systemic toxicity does not reference a specific recommendation made by the expert panel.⁹ The recommendation is to conduct an assessment of the how likely it is that enough data will be available to ensure that validation studies could go forward. Finally, she thinks SACATM meetings are improving and discouraged long PowerPoint presentations that distract from time for discussion. She also highly recommended ICCVAM and NICEATM distribute more background materials on ICCVAM nominations.

Dr. Rick Becker, American Chemistry Council, presented public comment via the telephone. He is pleased with the progress on the NTP Roadmap during the past year, especially with efforts to incorporate adequate attention to the evaluation and validation of methods.

C. SACATM Discussion

Dr. Goldberg congratulated Dr. Portier on the NTP Roadmap document. He said the statements on animal welfare and human science in the document are the strongest made by the U.S. government. However, the statements are in the middle of the document and he suggested NTP reference animal welfare concerns earlier in the document. He commented on two of the challenges of the NTP Vision. First, is how to set priorities for testing given that there are different strategies for priority setting. He suggested an early workshop to discuss priorities for testing. The second major challenge is how to make the large amount of data generated in this effort predictive for hazard.

Dr. Stephens was very supportive of the NTP Roadmap document and also thought references to animal welfare should appear earlier in the document. He especially liked references to physiologically based pharmacokinetic modeling, animal to human extrapolation, sensitive sub-populations, and the focus on humans, which he thinks will lead to the incorporation of human cell line assays. He understood that the evaluation and validation of these tests would likely incorporate a phase where they are used as adjuncts and therefore would not impact animal use in the short-term. He had a concern regarding the NTP Office of Nominations and its new rule to use expert judgment and predictive tools to guide research priorities. He asked how this office would interface with ICCVAM. Dr. Portier responded that the NTP has an immediate need to understand how to use mechanistic information to provide guidance on additional testing or test methods. He added that NTP nomination staff needs to become adept at using prediction tools to determine whether something is likely to be carcinogenic or acutely toxic. Further, these determinations will likely not be based on a single assay. Within NTP's structure, the Office of Nominations is the appropriate place for this to happen. The development of tools would occur elsewhere. With regard to Ms. Amundson comments, he noted that NTP is working closely with other agencies on similar efforts including EPA, FDA and NIOSH.

Dr. Stitzel appreciated the NTP Roadmap's emphasis on evaluating the data. In the past, she has been frustrated with NTP's role as a hazard identifier and welcomes interpretative guidance on how the data should be used to make risk assessment decisions.

Dr. Theran congratulated Dr. Portier on the leadership and creativity of the NTP Roadmap document. He suggested that explicit statements on animal welfare should appear more frequently in the document. Dr. Willhite thought a major challenge would be to limit the scope of the NTP Vision because there will be so many potential avenues to explore. He suggested working with ICCVAM to determine what tools need to be developed first. Dr. Sonnenshein expressed concern that increased reliance on mechanistic data could potentially lead to delays in making public health decisions until the mechanisms and their relationship to toxicology are

⁹ Note: this was a 2000 ICCVAM Workshop

understood. He stressed the need to critically evaluate the utility of the new approaches for making public health decisions.

IX. ICCVAM PERSPECTIVES ON THE PROPOSED OECD DRAFT GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT (GUIDANCE DOCUMENT 34)

Dr. Leonard Schectman (FDA) summarized the development of the current *OECD Draft Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment* (GD 34).

A. Meetings and Guidance Documents

Solna Workshops

The effort leading to GD34 began in 1994 when the National Coordinators for the OECD Test Guidelines Program agreed that OECD should make an attempt to internationally harmonize the available and evolving concepts directed towards the validation of alternative methods. Based on this recommendation, the OECD held a workshop in Solna, Sweden in January 1996 to discuss the topic (“Solna Workshop”). The overall purpose of the workshop was to attempt via the OECD to internationally harmonize the various published and advocated concepts for the validation of alternative methods. The scope was limited to emphasize alternative tests¹⁰ in the area of risk assessment for chemicals and chemical products. Consensus was reached at this workshop on several areas related to the principles and criteria for validation and regulatory acceptance, such as the criteria for a valid test and criteria for regulatory acceptance. In addition, workshop attendees reached consensus on several issues related to the validation process including definitions and reporting of results in peer-reviewed journals and to regulatory authorities. The final report of the Solna workshop was issued in September 1996 and formed the basis for early drafts of GD 34.

September 2001 OCED Draft Guidance Document (GD34) the Development, Validation, and Regulatory Acceptance of New and Updated Internationally Acceptable Test Methods in Hazard Assessment

In September 2001 the OECD released the first draft GD34. ICCVAM-ICCVAM submitted extensive comments on this draft. Some of the major points raised by ICCVAM-NICEATM are:

- Convene an international workshop to address issues in the GD (became the Stockholm Conference, March 2002).
- Draft GD34 does not, and should, comply with many recommendations of the 1996 Solna Workshop and workshop report. In addition, draft GD34 differs substantially from the 1996 Solna Workshop report in terms of content and organization.
- The proposed OECD procedure for validating alternative methods is cumbersome and costly and would yield few validated assays. In addition, there is insufficient guidance in GD34 for test sponsors regarding submission of adequate information and data.
- OECD should not imply itself to be the foremost validation authority and should acknowledge established organizations involved in the validation and regulatory acceptance of new test methods. The OECD should not propose that it serve as a formal authority for both international methods validation and regulatory acceptance. The OECD’s role should

¹⁰ Including aspects of all “Three Rs”: Replacement, Reduction, and Refinement

Minutes from the October 2004 SACATM Meeting

remain as an authority for methods harmonization that generates more flexible test guidelines based upon specific, standardized, validated procedures.

- The contents of the ICCVAM 1997 report “Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the Ad Hoc Interagency Coordinating Committee on the Validation of Alternative Methods” should be appended as appropriate to GD34.
- GD344 should include a discussion on the importance of understanding the mechanistic relevance of test methods.

OECD Conference on Validation and Regulatory Acceptance of New and Updated Methods in Hazard Assessment, Stockholm, Sweden, March 6-8, 2002 (“Stockholm Conference”)

The major aim of the Stockholm Conference was to develop consensus on “practical guidance on principles and processes for the validation and acceptance of animal and non-animal test methods for regulatory hazard assessment purposes,” such as the process for independent peer-review and management of the validation processes. Consensus achieved at the conference would then be used to revise draft GD34. Specific objectives were to provide practical guidance on:

- How to adequately address established validation principles and criteria.
- The conduct and management of the validation process.
- How to adequately address established principles and criteria for regulatory acceptance of validated test methods including the submission of information to support their validity.
- The process for independent peer review, regulatory consideration and implementation of new and updated test methods.

Dr. Schechtman listed approximately 20 noteworthy issues and recommendations of the Stockholm conference. Following the Stockholm meeting, a revised draft GD34 was released in October 2003, titled “OCED Draft Guidance Document (GD34) Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment.” Dr. Schechtman did not discuss the details of October 2003 draft because a newer version was released in September 2004, although he summarized ICCVAM’s comments on the draft.

September 2004 OCED Draft Guidance Document (GD34) Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment

Dr. Schechtman discussed the third draft GD34 released in September 2004. This draft was extensively revised and incorporates many of ICCVAM’s suggestions as well as comments and recommendations of other OECD member countries. Major revisions included changes to the table of contents, extensive revision of certain topics and the introduction of new topics. Overall, the changes broaden the document and reflect current thinking on the validation of test methods and their subsequent translation into OECD test guidelines. In addition, the changes make GD34 a more generic document and less prescriptive.

On October 13-15, 2004, OECD convened an expert panel consultation meeting (ECM) with two primary purposes. First, to resolve major differences between OECD member countries that would allow finalization of GD34. Second, to consider proposed modifications to the draft GD34 (21 September 2004) made by the OECD Secretariat and to further rework and improve the draft and ready it for National Coordinators of the OECD Test Guidelines Program (WNT) meeting in April or May 2005. Another specific objective was to discuss May 2004 WNT recommendations to broaden GD34 to include several other types of tests (e.g., biodegradation, ecotoxicology, *in vivo* and chronic testing) and discuss different approaches to validation employed by OECD

Minutes from the October 2004 SACATM Meeting

member countries. Dr. Schechtman said there is still considerable work to be done to revise GD 34, but consensus was achieved on many of the most controversial portions.

B. SACATM Discussion

Dr. Stitzel suggested SACATM concentrate on whether it agrees or disagrees with ICCVAM's comments on the different drafts of GD34 instead of discussing the specifics of the October 2003 draft disseminated as background material, because the October 2003 draft is out of date. Dr. Willhite noted that questions posed to SACATM often focus on providing guidance on how ICCVAM could promote or enhance activities related to alternative methods. He felt the most effective way to promote the use of alternatives is by proposing guidance that leads to cost-savings or by passing regulations and rules. However, he was not clear on the ICCVAM strategy for promoting alternatives in a manner that truly leads to implementation by regulatory agencies. Dr. Goldberg noted that past meetings on validation were framed to validate a set of tests against a set of reference standards by comparing the merits of each test against the reference standards; however, the anti-microbial ocular/dermal nomination appears to start from a different position. The anti-microbial approach would attempt to validate a battery of tests to look at a single chemical. He suggested SACATM discuss the issues associated with validating a battery of test for a single class of compounds rather than validating a single test against a variety of chemicals.

Dr. Smith complimented ICCVAM on its efforts on the GD 34. She recommended ICCVAM to continue the effort even though it may take considerable resources and time, because it will be very difficult to make changes when the international guidelines are accepted. Dr. Stitzel also commended ICCVAM efforts. She was concerned about the direction of the October 2003 draft and thought it appears that ICCVAM had a large role in affecting critical revisions to the most recent draft document. Dr. Halder commented that the comments on GD 34 also reflect the collaboration between ICCVAM and ECVAM who worked together to ensure their comments were complimentary. Dr. Stevens also noted the valuable role ICCVAM played in shepherding GD34. The current thrust is much improved and probably wouldn't have happened if ICCVAM had not had direct access to the OECD process; he encouraged continued direct access. Dr. Portier noted the role of EPA in this process. The National Coordinator for OECD activities resides at EPA in the Office of Pesticide Programs and Toxic Substances and it is through their interactions with ICCVAM that allowed ICCVAM to lead such this strong effort.

X. GENERAL DISCUSSION

Dr. Stitzel reiterated the need to have additional information on the ICCVAM nominations in the background materials for the meeting, or at least available on the Internet. In addition, Dr. Stitzel appreciated shorter presentations compared to previous meetings and wanted to encourage more time for discussion. She solicited suggestions for improvement. Dr. Willhite suggested ICCVAM and NICEATM put prioritized nominations into an overall context, in terms of where it came from, where does it fit in, and where will it go, to help understand the importance of the test method.

Dr. Stephens agreed that more information should be presented in the background materials to allow for more discussion time at the meeting. He also suggested agenda topics show more continuity between meetings where follow-up or related topics might be presented (e.g., the USDA *Leptospira* vaccine nomination). In response to concerns that the ICCVAM validation process is time consuming and expensive, he thought ICCVAM and SACATM could do more to promote the idea that the validation of alternative methods is good for science and animal welfare and that validation can be accomplished in a practical, nonburdensome manner. Dr. Curren also encouraged the distribution of more background materials for presentations of a quantitative nature such as the under-prediction analyses. For example, he found Dr. Haseman's notes on the

Minutes from the October 2004 SACATM Meeting

dermal irritation analysis to be more informative than the actual presentation. Also, he emphasized the need to distribute materials well in advance of the meeting.

In response to Dr. Stephens' comments about the perception of ICCVAM, Dr. Stitzel said the current process is a tremendous improvement over methods' validation prior to establishment of ICCVAM. Then there was really no process to get a test accepted that would have wide regulatory applicability. She believed the current process is working.

Dr. Sonnenshein suggested the NTP consider holding half-day, educational seminars adjacent to SACATM meetings on topics relevant to the development of alternative methods. Dr. Portier said NTP would consider this idea and welcomed receipt of potential topics.

Dr. Portier thanked Drs. Bucher and Wolfe for improving the NTP Roadmap document and Drs. Wind and Stokes for providing valuable feedback throughout the roadmap's development. Dr. Portier thanked NTP staff for organizing the meeting, EPA for use of its facility, and SACATM for their time and comments. He also thanked Dr. Stitzel for serving as Chair. Dr. Stokes thanked SACATM on behalf of ICCVAM and NICEATM and the public for attending. Dr. Stitzel thanked everyone on behalf of SACATM.

The meeting adjourned at 4:04 p.m.

Additional information regarding these materials is described in: Kamohara *et al.*, "Discoidin domain receptor 1 isoform-a (DDR1a) promotes migration of leukocytes in three-dimensional collagen lattices," *FASEB J.*, 15:2724-2726, 2001; Matsuyama *et al.*, "Interaction of discoidin receptor 1 isoform b (DDR1b) with collagen activates p38 mitogen-activated protein kinase and promotes differentiation of macrophages," *FASEB J.*, 17:1286-1288, 2003; Matsuyama *et al.*, "Activation of discoidin receptor 1 facilitates the maturation of human monocyte-derived dendritic cells through the TNF receptor associated factor 6/TGF-beta-activated protein kinase 1 binding protein 1beta/p38alpha mitogen-activated protein kinase signaling cascade," *J. Immunol.* 171:3520-3532, 2003; Matsuyama *et al.*, "Activation of discoidin domain receptor 1 isoform b with collagen up-regulates chemokine production in human macrophages: Role of p38 mitogen-activated protein kinase and NF-kB," *J. Immunol.* 172:2332-2340, 2004.

Method for Ex-Vivo Selection and Expansion of Stimulus-Responding Primary Cells Using Selective Reversible Immortalization

Eugene Barsov, David Ott (NCI)

U.S. Provisional Application No.: 60/528,244 filed 09 Dec 2003 (DHHS Reference No. E-210-2002/0-US-01).

Licensing Contact: Mojdeh Bahar; (301) 435-2950; baharm@mail.nih.gov.

This invention is a gene transfer technique to immortalize primary cells (e.g. lymphocytes) that respond to a stimulus, such as a viral antigen (e.g. HIV toxoids), a tumor antigen, or a growth factor. The antigen or growth factor stimulates a specific subset of primary cells within a population of cells to proliferate and divide. Murine leukemia virus (MuLV)-based retroviral vectors comprising a gene or genes for immortalization are used to transfect primary cells that have been stimulated to divide. Since MuLV retroviral vectors will only infect dividing cells, only primary cells activated by the antigen or growth factor will be infected by this retroviral vector and immortalized, thereby creating an "antigen-specific trap." The primary cells to be immortalized can be in targeted tissue or in stimulated *ex vivo* culture. The transduced cells are expanded to large numbers without differentiating, and brought back to the primary cell stage by removing the introduced genes (e.g. by Cre-lox recombination). The expanded population of primary cells can then be used.

Hybrid Adeno-Retroviral Vector for the Transformation of Cells

Changyu Zheng, Brian O'Connell, Bruce J. Baum (NIDCR)

U.S. Provisional Application No.: 60/265,198 filed 30 Jan 2001 (DHHS Reference No. E-312-2000/0-US-01; PCT Application PCT/US02/02279 filed 25 Jan 2002, which was published as WO 02/061104 on 30 Jul 2002 (DHHS Reference No. E-312-2000/0-PCT-02).

U.S. Patent Application No.: 10/470,784 filed 29 Jul 2003 (DHHS Reference No. E-312-2000/0-US-03).
Licensing Contact: Jesse Kindra; (301) 435-5559; kindraj@mail.nih.gov.

The invention described and claimed in these patent applications provides for novel hybrid vectors which may be used for cell transformation either *in vivo*, *in vitro*, or *ex vivo*. The hybrid vectors, which are capable of integrating into the chromosome of the host cell and are capable of transducing dividing and non-dividing cells, have an adenoviral serotype 5 backbone and two retroviral (Moloney murine leukemia virus) elements upstream and downstream of the transgene. These elements include part of the envelope sequence, the long terminal repeat (LTR) and the packaging signal sequence (upstream), and part of the envelope sequence and LTR (downstream). Due to their hybrid nature, these vectors provide a means of efficient, reliable, long-term gene expression. Furthermore, unlike other chimeric or hybrid vector systems, only a single vector is required to deliver a transgene of interest and retroviral functional proteins are not required. The vectors are packaged and delivered via an adenoviral particle and administered directly to the target cell.

This research is described, in part, in: Zheng *et al.*, "Inclusion of Moloney murine leukemia virus elements upstream of the transgene cassette in an E1-deleted adenovirus leads to an unusual genomic integration in epithelial cells," *Virology* 2003 313:460-72, 2003; Zheng *et al.*, "Integration efficiency of a hybrid adenoretroviral vector," *Biochem Biophys Res Commun.* 300:115-20, 2003; Zheng & Baum, "Long-term expression after infection by the hybrid vector AdLTR-luc is from integrated transgene," *Biochem Biophys Res Commun.* 291:34-40, 2002.

Dated: August 31, 2004.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 04-20295 Filed 9-7-04; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institute of Environmental Health Sciences; Notice of a Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) on October 20, 2004, at the U.S. Environmental Protection Agency (EPA), 109 TW Alexander Drive, Durham, NC (Building C, Room C111, Auditorium sections A. and B). The SACATM provides advice on the statutorily mandated duties of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the activities of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

The meeting is being held on October 20, 2004, from 8:30 a.m. until adjournment and is open to the public with attendance limited only by the space available. Individuals who plan to attend are strongly encouraged to register with the NTP Executive Secretary by October 13, 2004, in order to ensure access to the EPA campus (Dr. Kristina Thayer at the NTP Liaison and Scientific Review Office, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709; telephone: 919-541-5021; facsimile: 919-541-0295; or e-mail: thayer@niehs.nih.gov) or online on the NTP Web site (<http://ntp-server.niehs.nih.gov>) under "What's New." A map of the EPA campus, including visitor parking, is available at <http://www.epa.gov/rtp/transportation/parking/map.htm>. Please note that a photo ID is required to access the EPA campus.

Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, are asked to notify the NTP Executive Secretary at least seven business days in advance of the meeting (see contact information above).

Agenda

A preliminary agenda is provided below. A copy of the agenda, committee roster, and any additional information, when available, will be posted on the

NTP Web site (<http://ntp-server.niehs.nih.gov>) under "What's New" or available upon request to the NTP Executive Secretary (contact information provided above). Additional information about SACATM is available through the NICEATM/ICCVAM Web site (<http://iccvam.niehs.nih.gov>) under "Advisory Committee." Following the meeting, summary minutes will be prepared and available at this Web site and upon request to the NTP Liaison and Scientific Review Office (contact information above).

Preliminary Agenda

Scientific Advisory Committee on Alternative Toxicological Methods, October 20, 2004. U.S. Environmental Protection Agency, Building C, Room C111 (Auditorium sections A. and B), 109 TW Alexander Drive, Durham, NC 27709. (A photo ID is required to access the EPA campus.)

October 20, 2004

8:30 a.m.

- Call to Order and Introductions.
- Welcome and Remarks from the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP).
- Welcome and Remarks from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Chair.
- Update on Activities of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and ICCVAM.
- Update on the European Center for the Validation of Alternative Methods (ECVAM) Workshop Recommendations and Validation Studies.
- Evaluation of the Under-Prediction Rate for the *In Vivo* Rabbit Dermal Irritation Test.
- Public Comment.
- Evaluation of the Under-Prediction Rate for the *In Vivo* Rabbit Ocular Irritation Test.
- Public Comment.

12 p.m.

Lunch break (on your own, the EPA campus has a cafeteria).

1 p.m.

- ICCVAM Nominations.
- Public Comment.
- NTP Roadmap.
- Public Comment.
- ECVAM-ICCVAM-NICEATM Workshop on Validation of Toxicogenomic-Based Test Systems.
- General Discussion.

4:30 p.m. Adjourn

Public Comment Welcome

Public input at this meeting is invited and time is set aside for the presentation of public comments on any agenda topic. Each organization is allowed one time slot per agenda topic. At least 7 minutes will be allotted to each speaker, and if time permits, may be extended to 10 minutes. In order to facilitate planning for this meeting, persons wishing to make an oral presentation are asked to notify the NTP Executive Secretary (contact information above) by October 13, 2004, and to provide their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any). Registration to present oral public comments or to submit written comments can be completed online at the NTP Web site (<http://ntp-server.niehs.nih.gov>) under "What's New." Registration for oral comments will also be available on-site, although time allowed for presentation by on-site registrants may be less than that for pre-registered speakers and will be determined by the number of persons who register at the meeting.

Persons registering to make oral comments are asked, if possible, to provide a copy of their statement to the NTP Executive Secretary (contact information above) by October 13, 2004, to enable review by the SACATM and NIEHS/NTP staff prior to the meeting. Written statements can supplement and may expand the oral presentation. If registering on-site and reading from written text, please bring 40 copies of the statement for distribution to the SACATM and NIEHS/NTP staff and to supplement the record. Written comments received in response to this notice will be posted on the NTP Web site (<http://ntp-server.niehs.nih.gov>) under "What's New". Persons may also submit written comments in lieu of making oral comments. Written comments should be sent to the NTP Executive Secretary and received by October 13, 2004, to enable review by the SACATM and NIEHS/NTP staff prior to the meeting. Persons submitting written comments should include their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any) with the document.

Background

The SACATM was established January 9, 2002, to fulfill section 3(d) of Public Law 106-545, the ICCVAM Authorization Act of 2000 (42 U.S.C. 2851-3(d)) and is composed of scientists from the public and private sectors (**Federal Register**: March 13, 2002: vol. 67, no. 49, page 11358). The SACATM provides advice to the Director of the

NIEHS, the ICCVAM, and the NICEATM regarding statutorily mandated duties of the ICCVAM and activities of the NICEATM. The committee's charter is posted on the Web at <http://iccvam.niehs.nih.gov> under "Advisory Committee" and is available in hard copy upon request from the NTP Executive Secretary (contact information above). Information about NICEATM and ICCVAM activities can also be found at the NICEATM/ICCVAM Web site (<http://iccvam.niehs.nih.gov>) or by contacting the Director of NICEATM, Dr. William Stokes (telephone: 919-541-2384, or e-mail: niceatm@niehs.nih.gov).

Dated: August 26, 2004.

Samuel Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 04-20292 Filed 9-7-04; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF HOMELAND SECURITY

Office of the Secretary

Homeland Security Advisory Council

AGENCY: Office of the Secretary, Department of Homeland Security.

ACTION: Notice of Federal Advisory Committee meeting.

SUMMARY: The Homeland Security Advisory Council (HSAC) will hold its next meeting in Washington, DC on Wednesday, September 22, 2004. The HSAC will meet for purposes of (1) receiving reports from Senior Advisory Committees; (2) receiving briefings from DHS staff on Departmental initiatives; and (3) holding roundtable discussions with and among HSAC members.

This meeting will be partially closed; the open portions of the meeting for purposes of (1) above will be held at the U.S. Coast Guard Headquarters, 2100 Second Street, SW., Washington, DC, from 9:30 a.m. to 11:15 a.m. The closed portions of the meeting, for purposes of (2) and (3) above will be held at the U.S. Coast Guard Headquarters from 8:30 a.m. to 9:20 a.m. and from 11:30 a.m. to 3:30 p.m.

Public Attendance: A limited number of members of the public may register to attend the public session on a first-come, first-served basis per the procedures that follow. Security requires that any member of the public who wishes to attend the public session provide his or her name, social security number, and date of birth no later than 5 p.m., EST, Wednesday, September 15, 2004. Please provide the required

Attachment 2

AGENDA

**SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS
OCTOBER 20, 2004
ENVIRONMENTAL PROTECTION AGENCY (EPA)
BUILDING C (ROOM C-111)
RESEARCH TRIANGLE PARK, NC**

Wednesday, October 20, 2004

8:30 AM	Call to Order and Introductions	Dr. Jack Dean, Sanofi-Synthelabo, Inc., Chair
8:40 AM	Welcome and Remarks From the NIEHS/NTP	Director, NIH/NIEHS Dr. Christopher Portier, NIH/NIEHS
8:50 AM	Welcome and Remarks from the Chair, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)	Dr. Leonard Schechtman, NCTR/FDA
8:55 AM	Housekeeping	Dr. Kristina Thayer, NIH/NIEHS
9:00 AM	Update on Activities of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and ICCVAM	Dr. William Stokes, NIH/NIEHS
9:30 AM	Update on ECVAM Workshop Recommendations and Validation Studies	Dr. Thomas Hartung, ECVAM
9:55 AM	Break	
10:10 PM	Evaluation of the Under-Prediction Rate for the <i>In Vivo</i> Rabbit Dermal Irritation Test <ul style="list-style-type: none">• Public Comment• Committee Discussion	Dr. William Stokes, NIH/NIEHS Dr. Joe Haseman, consultant
11:10 PM	Preliminary Evaluation of the Under-Prediction Rate for the <i>In Vivo</i> Rabbit Ocular Irritation Test <ul style="list-style-type: none">• Public Comment• Committee Discussion	Dr. William Stokes, NIH/NIEHS Dr. Joe Haseman, consultant
12:10 PM	Lunch	
1:10 PM	ICCVAM Nominations <ul style="list-style-type: none">• Public Comment• Committee Discussion	Dr. William Stokes, NIH/NIEHS
1:45 PM	NTP Roadmap	Dr. Christopher Portier, NIH/NIEHS

- Public Comment
- Committee Discussion

2:45 PM Break

3:00 PM ICCVAM Perspectives on Proposed OECD Draft guidance Document on the Validation and International Acceptance of New or Updated Test methods for Hazard Assessment (Guidance Document 34) Dr. Leonard Schechtman, FDA/NCTR

4:00 PM SACATM General Discussion

~ 4:30 PM Adjourn

Attachment 3

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

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Attachment 4

Interagency Coordinating Committee on the Validation Of Alternative Methods (ICCVAM) Designated Agency Representatives

Agency for Toxic Substances and Disease Registry

- William Cibus, Ph.D.
- ◇ Moiz Mumtaz, Ph.D.

Consumer Product Safety Commission

- Marilyn L. Wind, Ph.D. (Vice-Chair)
- * Kailash C. Gupta, D.V.M., Ph.D.
- * Patricia Bittner, M.S.
- * Susan Aitken, Ph.D.

Department of Agriculture

- Jodie Kulpa-Eddy, D.V.M.
- ◇ Elizabeth Goldentyer, D.V.M.

Department of Defense

- Robert E. Foster, Ph.D.
- ◇ Patty Decot
- * Harry Salem, Ph.D.
- * John M. Frazier, Ph.D.

Department of Energy

- Marvin E. Frazier, Ph.D.
- ◇ Marvin Stodolsky, Ph.D.

Department of the Interior

- Barnett A. Rattner, Ph.D.
- ◇ Sarah Gerould, Ph.D.

Department of Transportation

- George Cushmac, Ph.D.
- ◇ Steve Hwang, Ph.D.

Environmental Protection Agency

- Joseph J. Merenda, Jr.
Office of Pollution Prevention and Toxics
Angela Auletta, Ph.D.
Office of Science Coordination and Policy
- ◇ Karen Hamernik, Ph.D.
Office of Research and Development
- ◇ Harold Zenick, Ph.D.
- * Suzanne McMaster, Ph.D.
OECD Test Guidelines Program
- * Maurice Zeeman, Ph.D.
Office of Pesticide Programs
- * Amy Rispin, Ph.D.
- * Deborah McCall

Food and Drug Administration

- Leonard M. Schechtman, Ph.D. (Chair)
- ◇ Suzanne C. Fitzpatrick, Ph.D., D.A.B.T.
Center for Drug Evaluation and Research
- * Abigail C. Jacobs, Ph.D.
Center for Devices and Radiological Health
- * Raju Kammula., D.V.M., Ph.D., D.A.B.T.
- * Melvin E. Stratmeyer, Ph.D.
Center for Biologics Evaluation and Research
- * Richard McFarland, Ph.D., M.D.
Center for Food Safety and Nutrition
- * David G. Hattan, Ph.D.
- * Robert L. Bronaugh, Ph.D.
Center for Veterinary Medicine
- * Devaraya Jagannath, Ph.D.
- ◇ C. Miriam Aguila, D.V.M.
National Center for Toxicological Research
- * William T. Allaben, Ph.D.
- * Martha M. Moore, Ph.D.
Office of Regulatory Affairs
- * Atin R. Datta, Ph.D.

National Cancer Institute

- Alan Poland, M.D.
- ◇ Marjorie C. Strobel, Ph.D.

National Institute of Environmental Health Sciences

- William S. Stokes, D.V.M., D.A.C.L.A.M.
- ◇ John R. Bucher, Ph.D., D.A.B.T.
- * Rajendra S. Chhabra, Ph.D., D.A.B.T.
- * Jerrold J. Heindel, Ph.D.

National Institute for Occupational Safety and Health

- Paul Nicolaysen, V.M.D.
- ◇ Douglas Sharpnack, D.V.M., M.S., D.A.C.V.P.

National Institutes of Health

- Margaret D. Snyder, Ph.D.
- ◇ Nelson Garnett, D.V.M., D.A.C.L.A.M.

National Library of Medicine

- Vera Hudson, M.S.
- ◇ Jeanne Goshorn, M.S.

Occupational Safety and Health Administration

- Surender Ahir, Ph.D.

- Principal Agency Representative
- ◇ Alternate Principal Agency Representative
- * Other Agency Representative