Summary Minutes SACATM Meeting
September 16, 2014
NIEHS, Research Triangle Park, NC

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I. Location of Background Materials/Presentations and Frequently Used Abbreviations

Background materials and presentations for the 2014 Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting are available on the SACATM meeting website (http://ntp.niehs.nih.gov/go/8202)

3Rs	Replacement, reduction, and refinement (causing less pain and distress) in the use of animals for toxicological testing
ADME	absorption, distribution, metabolism, and excretion
AOP	Adverse Outcome Pathway
AR	androgen receptor
CAAT	Center for Alternatives to Animal Testing
CHO	Chinese Hamster Ovary
CPSC	Consumer Product Safety Commission
DABT	Diplomate of the American Board of Toxicology
DOI	Department of the Interior
DPRA	Direct Peptide Reactivity Assay
EASA	electrophilic allergen screening assay
EDC	endocrine disrupting chemicals
EDSP	Endocrine Disruptor Screening Program
EPA US	Environmental Protection Agency
ER	estrogen receptor
EU	European Union
EURL ECVAM	European Union Reference Laboratory for Alternatives to Animal Testing
FDA	U.S. Food and Drug Administration
HIST	histamine sensitization test
HT	high throughput
HTS	high throughput screening
ICATM	International Cooperation on Alternative Test Methods
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICH	International Conference on Harmonization
ILS	Integrated Laboratory Systems, Inc.
IVIVE	*in vitro* to *in vivo* extrapolation
JaCVAM	Japanese Center for the Validation of Alternative Methods
KoCVAM	Korean Center for the Validation of Alternative Methods
LLNA	Local Lymph Node Assay
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIH	National Institutes of Health
NLM	National Library of Medicine
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
OPP	Office of Pesticide Program
PCRM	Physicians Committee for Responsible Medicine
PETA	People for the Ethical Treatment of Animals
QSAR	quantitative structure-activity relationship

SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SBIR	Small Business Innovative Research
SNP	single nucleotide polymorphisms
SSS	Social and Scientific Systems, Inc.
STTR	Small Business Technology Transfer
USDA	U.S. Department of Agriculture

II. Attendance

SACATM met on September 16, 2014, at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. The following individuals attended the meeting:

SACATM
Lauren Black, PhD, Charles River Laboratories
Joy Cavagnaro, PhD, DABT, RAC, ATS, RAPS, AccessBIO, L.C.
William Janzen, UNC-Chapel Hill
Safdar Khan, DVM, MS, PhD, DABT, ASPCA
Ricardo Ochoa, DVM, PhD, ACVP, Pre-Clinical Safety, Inc.
Catherine Willett, PhD, The Humane Society of the United States
Daniel Wilson, PhD, DABT, The Dow Chemical Company (chair)
Wei Xu, PhD, University of Wisconsin at Madison

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Principal Representatives
Surender Ahir, PhD, Occupational Safety and Health Administration (by telephone)
Carol Clarke, DVM, DACLAM, U.S. Department of Agriculture (USDA, by telephone)
Bert Hakkinen, PhD, National Library of Medicine (NLM)
Abigail Jacobs, PhD, U.S. Food and Drug Administration (FDA, ICCVAM Co-Chair)
Anna Lowit, PhD, U.S. Environmental Protection Agency (EPA, ICCVAM Co-Chair)
Joanna Matheson, PhD, U.S. Consumer Product Safety Commission (CPSC)
Moiz Mumtaz, PhD, Agency for Toxic Substances and Disease Registry
Karen Taylor, DVM, National Institute for Occupational Safety and Health (NIOSH)
Barnett Rattner, PhD, Department of the Interior (DOI, by telephone)
Nigel Walker, PhD, DABT,) Deputy Division Director for Science, Division of NTP

Other ICCVAM Representatives
Warren Casey, PhD, DABT, Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
David Dix, PhD, EPA (by telephone)
Richard McFarland, MD, PhD, FDA/Center for Biologics Evaluation & Research

International Cooperation on Alternative Test Methods (ICATM) Representatives
Hajima Kojima, Japanese Center for Validation of Alternative Methods

Tae Sung Kim, Korean Center for Validation of Alternative Methods
Michele Regimbald-Krnel, Health Canada
Won Keun Seong, Korean Center for Validation of Alternative Methods
Valerie Zuang, European Union Reference Laboratory for Alternatives to Animal Testing, EURL ECVAM

NIEHS/NIH Staff
Mamta Behl, PhD, DABT
Linda Birnbaum, PhD, DABT, ATS, NIEHS/NTP Director
John Bucher, PhD, DABT, NTP Associate Director
Michael DeVito, PhD
Dori Germolec, PhD
Robbin Guy
Robin Mackar
Elizabeth Maull, PhD
Sri Nadadur, PhD
Richard Paules, PhD
Keith Shockley, PhD
Christina Teng, PhD
Mary Wolfe, PhD, Deputy Division Director for Policy, DNTP
Lori White, PhD, PMP, Designated Federal Officer

Bridport Services, LLC
Ernie Hood, MA

Integrated Laboratory Systems, Inc. (ILS, NICEATM support contractor) Staff
David Allen, PhD
Neepa Choksi, PhD
Jonathan Hamm, PhD
Nicole Kleinstreuer, PhD
Steven Morefield, MD
Michael Paris
William Polk
Catherine Sprankle
Judy Strickland, PhD, DABT

Public
Patricia Bishop, People for the Ethical Treatment of Animals (PETA, by telephone)
Yoshihito Deguchi
MeiChun Lai, PhD, Physicians Committee for Responsible Medicine (PCRM)
Jason Pirone, Social and Scientific Systems, Inc. (SSS)
Marjo Smith, SSS
Kristie Sullivan, PCRM (by telephone)
Marjolein Smith, PhD, ASI
Beth Warren Koncicki

Webcast Participants
Barun Bhhtarai, The Dow Chemical Company
Dave Gossai, Avon
Diego Rua, FDA
Elizabeth Baker, Center for Responsible Science
Geoff Patton, PhD, FDA
Ian Gilmour, EPA
Jessica Sandler, PETA
Jeanne Goshorn, NLM
Kamin Johnson, The Dow Chemical Company
Katherine Groff, PETA
Kristi Pullen, Natural Resources Defense Council
Raja Settivari, The Dow Chemical Company
Suzanne Davis, Department of Toxic Substances Control
Tami Drake, Center for Responsible Science
Xiaoqing Chang, ILS
Ying Huang, FDA

III. Welcome and Opening Remarks

SACATM Chair Dr. Daniel Wilson called the meeting to order at 8:30 AM. All in attendance introduced themselves. Dr. Wilson welcomed the new SACATM members, William Janzen, Catherine Willett, and Wei Xu. He noted that SACATM members Drs. Tracie Bunton, Joan Chapdelaine, Mark Evans, and Michael Kastello were unable to attend the meeting.

Dr. Linda Birnbaum, NIEHS/NTP Director, welcomed everyone to the meeting, including International Cooperation on Alternative Test Methods (ICATM) representatives Hajima Kojima, Tae Sung Kim, Michele Regimbald-Krnel, Won Keun Seong, and Valerie Zuang. She noted that it had been just over one year since the release of the new vision and direction for ICCVAM (15 Years Out: Reinventing ICCVAM), an *Environmental Health Perspectives* article that outlined a reorganization and new focus for the 15-member committee. She said that throughout this meeting, SACATM members would hear about the significant progress that had been made on a variety of fronts since the plan was released. Most importantly, she said, would be the description of ICCVAM's new "fit-for-purpose" approach to validation, which focuses more on the needs of the individual agencies and industries that are best positioned to quickly adopt a specific alternative test method. She noted also that the change and expansion in the role of NICEATM would be described. She was very pleased to see the many collaborations that have developed between agencies, industries, and international partners, which were exactly the types of activities envisaged with the passage of the original ICCVAM Authorization Act 15 years ago. She thanked the outgoing SACATM members and presented each one with a certificate and letter of appreciation.

Dr. Warren Casey, NICEATM Director, welcomed everyone to the meeting, and highlighted two overarching themes for the event: the unprecedented level of collaborations being conducted and the sense of urgency being applied to all projects, with most projects on an aggressive timeline of one year, reflecting the fit-for-purpose validation approach.

NTP Associate Director Dr. John Bucher added his welcome, noting that the activities to be described at the meeting are part of a larger effort across the NTP to begin to pull together elements of a new science designed to be quicker and less expensive while being as or more accurate than previous science in predicting human health outcomes.

Designated Federal Officer Dr. Lori White read the conflict of interest statement for SACATM.

IV. Update on ICCVAM Activities

A. Review of ICCVAM Vision/EPA Oral-Dermal

Dr. Anna Lowit, EPA and ICCVAM Co-chair, began the ICCVAM update with a review of the ICCVAM vision and direction that had been introduced one year ago, combined with an update on the NICEATM/EPA Oral-Dermal collaboration focused on acute oral and dermal toxicity testing.

She highlighted three projects that have benefited from the new approach aimed at short-term gains and described the collaboration between NICEATM and the EPA Office of Pesticide Programs (OPP). These collaborations are designed to evaluate the relative contribution of acute and dermal toxicity tests in providing information related to labeling of pesticides, with the hope that animal use in those areas could be significantly reduced. The project consists of three steps: (1) compilation of datasets of oral and dermal LD_{50} studies, (2) comparison analysis of the results of the tests, (3) and analysis of implications – whether both the oral and dermal LD_{50} tests are needed for labelling. Both technical chemical product and formulations are tested, with the top six required studies being referred to as the “six-pack.” The acute data are often used to determine personal protective equipment required for workers handling pesticides. The project is ongoing, with large amounts of data having been collected, focusing on formulations where the greatest potential reduction in animal use is to be found. Dr. Lowit noted that the project is currently in the second step, the comparison of results of acute and dermal LD_{50} tests. The project will be ready for public comment by fall 2014, including the dataset and statistical analysis. Dr. Lowit concluded by mentioning that EPA-OPP and NICEATM are in the early stages of a multi-stakeholder, collaborative project to expand the use of *in vitro* studies in skin sensitization, dermal irritation, and skin irritation.

B. USDA – Animal Reductions in *Leptospira* Vaccine Testing

Dr. Carol Clarke, USDA, updated SACATM on progress over the past year to reduce hamster usage in *Leptospira* vaccine potency testing. The plan is to follow animal use reduction trends for the next five years, providing yearly progress updates. She described the testing requirements, procedures, and how the animals are used. The animals are used not only to test vaccines but also to cultivate and propagate virulent strains for the testing program. Alternative tests must be considered under the Animal Welfare Act. The Center for Veterinary Biologics (CVB) developed and validated an *in vitro* Enzyme-linked Immunosorbent Assay (ELISA) antigen quantification method. Manufacturer exemptions to allow use of the ELISA are available under a guidance document; however, the USDA cannot require companies to use the ELISA test. Another challenge is that the CVB must perform confirmatory tests in the same way the manufacturer did, often necessitating the use of live animals. The proliferation of the ELISA test remains a challenge, as does compilation of an annual animal use report. Dr. Clarke described the role to be played in meeting those challenges by the CVB, Animal Care, and the Animal Welfare Information Center.

C. CPSC/EPA/FDA/NTP – Skin Sensitization Working Group Activities

Dr. Joanna Matheson, Consumer Product Safety Commission (CPSC), updated SACATM on activities over the past year conducted by the Skin Sensitization Working Group. The group has concentrated on four areas:

1. Consideration of criteria for ICCVAM acceptance of ECVAM individually validated skin sensitization methods.
2. Design and examination of the predictive value of a battery of ECVAM-validated methods and of *in silico* methods based on statistical methods.
3. A review of the battery for dermal sensitization recommended by Cosmetics Europe.
4. Disposition of the NIOSH Electrophilic Allergen Screening Assay (EASA) nomination.

Dr. Matheson described the EURL ECVAM validations and recommendations, including Direct Peptide Reactivity Assay (DPRA), Myeloid U937 Skin Sensitization Test, Human Cell Line Activation Test, and KeratinoSens™.

She also reported on the ICCVAM proposal to produce and test an integrated decision strategy for skin sensitization, using physicochemical parameters, an *in silico* method, and the three *in chemico* or *in vitro* assays validated by EURL ECVAM. She said the model could be developed relatively quickly and tested under regulatory conditions.

Dr. Janzen asked if there is a liver microsome metabolism test as part of the skin sensitization program and Dr. Matheson replied no.

Dr. Willett asked if there were any opportunity for prospective validation in the skin sensitization study, and said she was glad to hear that structural alerts were being considered. She asked about the issue of pesticide formulations, as there were not many in the validation studies. Dr. Matheson said formulations are a concern beyond just pesticides. She said there are some formulations in the data set. Dr. Casey added that ICCVAM is not organized or funded to do external validation studies, and the problem is not unique to the U.S. He said ECVAM is leading efforts in validation of skin sensitization alternative methods, and hopefully that work will progress to the point where prospective studies are needed, with validated protocols. She noted that there are currently several assays being investigated, and that some of them without the large datasets may provide better answers going forward. Dr. Jacobs said for formulations to be tested, a 3D skin model assay would be needed. Dr. Zuang said a 3D model SENS-IS®, an EPISKIN® based model for identifying chemical sensitizers, is being developed. Dr. Casey noted that this would be one of the topics of discussion at the upcoming ICATM meeting.

Dr. Khan asked Dr. Matheson whether the EASA assay only covers one pathway. Dr. Matheson said it is mechanistically similar to the DPRA assay and is solely based on chemical binding to model hard or soft electrophiles. Like the DPRA, it does not have a metabolism step, but a metabolism step could be incorporated into the assay.

Dr. Casey said the skin sensitization project would serve as a model system for how to conduct validation, in general, going forward. He added that the choice of a reference material remains challenging.

D. Public Comment

Ms. Patricia Bishop, PETA, commented by telephone. She said that PETA is very pleased with ICCVAM's new direction and its much stronger focus on achieving real reductions in animal use. She said Dr. Casey has been responsive to stakeholders and proactive in devising effective actions to implement the 3Rs. She also praised the 2012-2013 ICCVAM Biennial Report and expressed appreciation of ICCVAM's enhanced outreach and communications efforts. Although pleased with ICCVAM's work with the global community on developing new alternative test methods, she said that PETA believes that further work is needed in that area, particularly by enhancing collaboration with ICATM. PETA recommends that ICCVAM should include routine revisions and updates to its test method recommendations to member agencies.

Regarding the expansion of international harmonization issue, Dr. Casey said more than just validation needs to be done, with much larger policy issues at stake, particularly standards of accepting data. He said that although that is outside the scope of ICATM, NICEATM and ICCVAM certainly hope to facilitate the process, and he noted that the issue is on the agenda for the ICATM meeting.

E. SACATM Discussion

Dr. Ochoa, lead discussant, commented that as this was his last meeting it was his final opportunity to address his fellow SACATM members. Regarding ICCVAM's progress in carrying out the work described in the vision and strategy document, he said his impressions were very positive about ICCVAM. He noted ICCVAM's improvement in communications and praised Dr. Casey for his efforts in that area. He asked for more discussion about the PETA/PCRM query about endocrine disruption and thyroid disruption models, and ICCVAM's responses to inquiries about the use of fish embryos as an alternative to some of the current models of toxicological testing. Regarding additional short- to intermediate-term scientific areas that ICCVAM and NICEATM should pursue, he noted that ICCVAM has accomplished multiple positive results in reducing the number of animals used in the process of meeting regulatory requirements for product registration. He said increased collaborations have produced tangible results. He proposed carcinogenicity assessment as an area for expanded attention. Carcinogenicity assessment studies have been conducted in rats and mice since the 1950s, and rely on the premise that they are predictive of carcinogenicity in humans. He said the reality is very different, as the animal models are over-predictors of human risk. He described the history of carcinogenicity studies in more detail, including the advent of genotoxicity studies. He proposed that ICCVAM accept leadership in the area by convening a study group to gather regulators, academic scientists, and industry scientists to examine the ongoing need for carcinogenicity studies, which use hundreds of animals, are expensive, take a long time, and may be obsolete.

Dr. Jacobs said she agreed with Dr. Ochoa's point about carcinogenicity studies. She noted that the International Conference on Harmonization (ICH) is conducting a project involving waivers of rat and mouse studies, with blinded information being considered for its predictive value. Dr. Ochoa indicated the need for the whole strategy of carcinogenicity assessment to be re-evaluated with participation by scientists from across the spectrum. Dr. Jacobs said it is recognized by many that some of the rodent findings are not relevant to humans.

Dr. Casey said the zebrafish embryo is a model being examined, with two workshops this year alone. He agreed with Dr. Ochoa's proposal about carcinogenicity studies. He said that hopefully it would be on ICCVAM's work plan soon, and NTP is also very interested. He noted that through the Small Business Innovative Research (SBIR) plan, technologies to make use of archived tissues are being developed.

Dr. Cavagnaro noted the success in development of biologics without the need for mouse and rat carcinogenicity studies. She said there is progress in the area and pharmaceutical companies are involved. She asked Dr. Clarke whether there would need to be a regulatory requirement for stakeholders to use the ELISA assay. Dr. Clarke replied that the only way to make it a requirement would be to make it mandatory, which is a process that could take many years. She said USDA is always looking for non-regulatory solutions because faster results are achieved. By making the process easier, companies might be more willing to use the ELISA test on a regular basis. Dr. Khan noted that the ICATM recommendations are not binding by

law. Dr. Clarke said the CVB certainly has done a great deal of the work trying to get the ELISA test globally accepted.

Dr. Lowit noted that EPA's OPP now requires zebrafish studies.

Dr. Willett said over the last couple of years, ICCVAM had done "an amazing job" of addressing structural issues, with greatly improved collaboration and communication. She noted that OECD has ongoing activities in thyroid disruption and carcinogenicity study methods. She said the role of ICATM could be much stronger in coordinating the activities of OECD and facilitating global harmonization of regulatory needs. Dr. Casey said in the upcoming ICATM meeting, those issues would be addressed.

Dr. Bucher said the issue of cancer bioassays is somewhat different in environmental science than in the pharmaceutical industry. He said the assays are costly and issues related to verification of assay outcomes versus human health outcomes are becoming more and more difficult, because fewer epidemiological studies are being conducted. In areas where there are epidemiological studies, more verification of the animal study findings is being seen. He agreed that acceptance of shorter-term carcinogenicity studies by all stakeholders would be a tremendous advance. Dr. Ochoa agreed with Dr. Bucher's comment that one solution would not fit every agency and every need, which is why he was not calling for elimination of carcinogenicity studies, just suggesting that the topic be addressed to see how improvements could be made.

Dr. Xu wondered if genomic data, such as single nucleotide polymorphisms (SNPs) and key metabolic enzymes of importance for metabolic activation in some of the carcinogenicity pathways might be used as surrogates for the standard carcinogenicity studies.

In summary, Dr. Wilson said there appeared to be a fairly uniform sense that there was a resounding success across ICCVAM's efforts in a remarkably short period of time. As to whether there may be new areas for ICCVAM's attention, it should continue to be a priority to determine how carcinogenicity testing can be streamlined and improved to result in reduced animal use. Generally, there was agreement that ICCVAM's priority areas are where they should be, and that the near-term success has been remarkable, with ICCVAM being perceived as very receptive to further dialogue with stakeholder groups.

V. Update on ICCVAM Communication Activities

A. Presentation

Dr. Casey updated SACATM on ICCVAM communication activities over the past year. The ICCVAM vision document included plans to improve the ICCVAM and NICEATM websites and achieve broader engagement with the scientific community and stakeholders through several mechanisms. The websites have been integrated into the NTP website with consolidated

content, a new content management system, and added features such as a contact and dialogue mechanism and content on the 3Rs. Additionally, ICCVAM has instituted a new ICCVAM-all listserv and a new Adverse Outcomes Pathway Community listserv.

Dr. Casey listed four workshops conducted by ICCVAM over the past year, and three more planned for 2015. He noted key publications including the 2012-2013 ICCVAM Biennial Progress Report. He listed events designed to facilitate stakeholder engagement including the First Annual ICCVAM Public Forum, which was held June 25, 2014, and a Community of Practice webinar planned for January 2015. He said the plan is for at least three opportunities per year for interactions with stakeholders.

B. Public Comment

Dr. MeiChun Lai, PCRM, approved of ICCVAM's improved communication with stakeholders. She suggested improvements to the milestones table on the website.

C. SACATM Discussion

Dr. Wilson said ICCVAM communications efforts have noticeably improved in the recent past. He noted the website changes and new listservs, as well as other communication initiatives including workshops and stakeholder interaction opportunities. He recommended adding links to the ICCVAM website to some of the other associated entities such as ToxCast, Tox21, and the Animal Welfare Information Center. He said it was clear that the communication efforts and opportunities for interaction came about in response to feedback from SACATM, and that it showed that ICCVAM was very responsive and very receptive. He noted that it is important to understand that "we are all stakeholders." He described the vision for ICCVAM as an overhaul of the fundamental approach to toxicology testing, and it will necessitate making sure that everyone concerned is involved, as appropriate.

Dr. Willett suggested that ICCVAM get involved in some of the other related activities such as the Center for Alternatives to Animal Testing (CAAT), its communications group, and the Human Toxicology Project Consortium. Dr. Casey said CAAT is also involved with the use of systematic review to evaluate data, which is of great interest to NTP.

Dr. Ochoa said that despite the advances in communication by ICCVAM, the work itself is not very well known or understood outside a small group. He suggested that ICCVAM presentations should be widened to outline the work to organizations aside from the Society of Toxicology (SOT); targeting similar organizations in other disciplines. Dr. Casey said that was an approach ICCVAM could look into, and that a similar approach is being taken with respect to OECD.

D. Report on Outcome of ICCVAM Public Forum

Dr. Wilson briefed SACATM on the ICCVAM Public Forum, which he attended on June 25, 2014, as the SACATM representative. He said the purpose of the meeting was to serve as one of the three formal opportunities identified by ICCVAM for stakeholders and members of the public to provide input on ICCVAM programs. He noted that although the meeting was in June, much of what he had heard as plans then are now already being presented as results; the agencies are moving at a fast pace to accomplish what they outlined in their plans. He felt the meeting was an opportunity for meaningful input into some of the newer platforms such as skin sensitization, aiding their progress toward global acceptance. It became clear at the forum that the movement to alternative testing methods is very multi-faceted on a number of parallel fronts. He anticipated not just limited success in a few focused areas, but a much broader success across many agencies.

VI. Update on NICEATM Activities

A. Presentation

Dr. Casey presented an update of NICEATM's activities over the past year. NICEATM provides administrative and scientific support to ICCVAM and is organized as an office under the Division of the NTP within NIEHS. He said although the NICEATM operation has changed, its 15 years of experience in evaluating and validating alternative methods remains invaluable. NICEATM consists of two federal employees and other staff provided by the ILS support contract. He described the collaboration and support NICEATM now provides to Tox21, and noted that one of the goals of Tox21 involves reducing reliance on animal models.

He discussed the NICEATM focus areas: retrospective validation, high-quality reference data, analysis and validation of high throughput screening (HTS) data, integrated testing and decision strategies (ITDS), *in vitro* to *in vivo* extrapolation (IVIVE), development and validation of quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship models, alternative model systems, and metabolism. He characterized NICEATM as a service organization that helps agencies validate methods that they can then accept. Thus, fit-for-purpose validation is getting the right product to the right person at the right time, and getting the agencies what they need when they need it. There is much effort by NICEATM to provide high-quality results in a short period of time.

Dr. Casey illustrated some of the concepts he had been describing by reviewing their impact on a single project related to endocrine disruptors, a collaboration between NICEATM, EPA's National Center for Computational Toxicology (EPA NCCT), and EPA's Office of Science Coordination and Policy (EPA OSCP). The objectives of the project are to characterize the relationship between *in vitro* ER-pathway activity measured using Tox21 HTS assays and outcomes in uterotrophic animal studies in rodents, and to validate an HTS approach incorporating *in silico*, *in vitro*, and alternative animal models that can be used to prioritize or

even exclude chemicals from testing. He described the project in detail, including the development of a database of uterotrophic studies and comparisons between IVIVE studies and uterotrophic studies. He presented information about the current state of development of the zebrafish embryo model for toxicity testing and the movement toward incorporating metabolism data into Phase III of Tox21.

Going forward, NICEATM will focus on toxicity testing in endocrine disruptors, acute oral and inhalation testing, *in vitro* testing of nanomaterials, skin sensitization, and reproductive and developmental toxicity.

B. SACATM Discussion

Dr. Janzen, first discussant, said it is important to think carefully about how the term "validation" is being used, including what requirements will be for labs that generate *in vitro* data in terms of how they validate their assays. He said there would need to be some ongoing control and monitoring of those labs, because HTS assays can drift. He recommended that when NICEATM is organizing future workshops and symposia, groups reviewing the data and accepting validation should be included along with stakeholders. He noted that HTS is inherently designed to find positives, not negatives, so almost every assay is biased toward the positive, and that should be kept in mind when analyzing HTS outcomes or extrapolating from them. Dr. Casey replied that the data he had shown was a summary of 18 assays, lending higher confidence. He acknowledged that positives in HTS are a significant problem, which led to the amalgamation of 18 dose-response curves.

Dr. Xu, second discussant, noted, regarding future workshops and symposia, that currently many workshops are organized by topics specific to individual agencies' interests. She suggested that workshops be focused on methods developed for centralized biological systems, particularly toxicological methods in endocrine reproductive and developmental toxicity, acute and chronic toxicity, ocular toxicity, immune response, and vaccines. She said those areas are all quite different and would focus more on the biology.

Dr. Willett noted that it is very important to bring regulators into the process of developing workshops and the validation process itself. She wondered if there might be room to have agency-specific workshops to bring the regulators in on activities happening within an agency. Dr. Casey said EPA OSCP is driving the endocrine disrupter project because it is in direct support of its mission. This is an example of working directly with the regulators who might potentially use the information.

Dr. Cavagnaro asked for a definition of fit-for-purpose validation and noted the distinction between validation and acceptance. Dr. Casey said validation is, by definition, fit for purpose. He cited skin sensitization as an example of fit-for-purpose validation, with EPA having specific requirements that differ from other agencies. He said in the past, there would have been an attempt to develop a method that would meet everyone's needs; however, now, focusing on EPA, NICEATM is working to meet EPA's needs first.

Dr. Zuang commented that validation always occurs for a particular purpose, so she did not see much difference in the fit-for-purpose concept. Dr. Casey cited the example of the skin sensitization validation specific to EPA's needs.

Dr. Black said it is unclear to the public how sophisticated and specific many of the validations have been, and needs to be communicated more effectively, particularly on the ICCVAM website.

Dr. Lowit said validation is actually a continuum, from highly specific validations to more general ones. Fit-for-purpose validations fall within that spectrum. Dr. Casey agreed that with many of the HT methods, the method is being validated as well as the dataset, with an HT method being validated for a particular purpose for one particular agency. Thus, transferability is not an issue with such assays. Dr. Cavagnaro agreed that acceptance and implementation are inherently part of the fit-for-purpose paradigm. Dr. Casey noted that part of the intent is for agencies to reach a point where they would require a validated alternative test and would no longer accept animal test data.

Dr. Ochoa said validation needs to be very clear, because it is often difficult for people to accept that validations of methods designed to replace animal studies are applicable to their own specific circumstances.

Dr. Wilson stated that NICEATM accomplishes a great deal with very few people.

VII. Update on International Collaborations/ICATM and Interactions with ECVAM

A. Presentation

Dr. Casey said there are many misconceptions about ICATM, so to help resolve some of that confusion, at least among the partners, there was a meeting last year where all of the organizations described their organizational structures and their goals. He noted that although the organizations have similar names, their structures and goals are all completely different. He said a meeting report would be published soon.

Dr. Lowit briefed SACATM on international collaborations, harmonization, and adoption of alternative test methods, which are high priorities for ICCVAM. Regarding collaborations, she said that many good ideas are in place, and now implementation is needed.

She described the OECD Test Guidelines program, which is a mechanism for the international evaluation and adoption of alternative methods by its 34 member countries. She also discussed the organization of ICATM, which coordinates the validation and adoption of alternative methods among its members: the U.S., Canada, the European Union, Japan, and Korea. She provided more details on European Union Reference Laboratory for Alternatives To Animal Testing

(EURL-ECVAM), which is a mission-driven validation enterprise. Dr. Lowit mentioned that ICCVAM and NICEATM are working with EURL-ECVAM on a process to enable U.S. scientists to participate actively in the EURL-ECVAM test method evaluations, with U.S. designees being involved in each of the steps of the process from submission through validation study design to peer review and final recommendations. The goals are to get U.S. federal representation on assays with interested federal agencies and speed up ICCVAM responses to EURL-ECVAM recommendations. She described the EURL-ECVAM validation process, which is inherently collaborative. Part of the collaboration is to create a new ICCVAM process to overlap with the EURL-ECVAM process, allowing fuller integration. She illustrated how ICCVAM participation in the steps of the EURL-ECVAM would work at each level.

For 2105 and beyond, the overall ICCVAM goal for international coordination is to fully integrate in international efforts. Among other initiatives, the group will seek to nominate ICCVAM agency experts to international working groups, validation management teams, and organizing committees.

Dr. Lowit said although progress on reducing animal use involves multiple efforts on multiple fronts, international harmonization is a challenge that must be faced directly. In some cases, animal tests that are no longer required in the U.S. or Europe may still be required elsewhere and so are still being conducted. She said implementation of alternative methods on a global scale remains one of the great challenges facing the field.

B. Public Comment

Dr. Lai from PCRM thanked ICCVAM for taking an active role in collaborating with EURL-ECVAM. She said PCRM had identified some troubling existing gaps. Since member countries maintain their own national data requirements, some test methods become duplicative, with multiple studies being conducted for the same end point. This limits the options for animal use reduction for companies wishing to market a product in multiple countries or regions. She cited examples of the phenomenon, which had been included in PCRM's written comment. She encouraged ICATM to be more transparent so that regulators from other countries could easily contact ICATM members. She also detailed several steps by which ICATM could play a more active role in harmonization.

C. SACATM Discussion

Dr. Khan, first discussant, said the most active partner in harmonization and collaboration is EURL-ECVAM, with a well-defined process that ICCVAM has been following. He said cooperation is also happening in OECD countries, with their test guideline program, which provides a mechanism for international evaluation and adoption of alternative methods by 34 countries. He described the 2013 ICATM meeting in Tokyo, where cooperation in 5 areas was

agreed upon: validation studies, how to conduct peer review, how to achieve a harmonized approach to recommendations, communication and dissemination of information, and following a tracking system for alternative method QSARs.

He said some progress had been made since the establishment of ICATM in 2009, but still felt that ICCVAM could collaborate more, and that hopefully ICATM could include others such as South America, China, and Africa in the collaboration.

He described several of the test method recommendations from EURL ECVAM and the U.S. responses to them. The DPRA could be used in conjunction with other data, but should not be used as a stand-alone assay. He noted some of the advantages and limitations of the zebrafish embryo toxicity test and agreed with ICCVAM's recommendation. He said that the KeratinoSens™ test is a powerful tool, but is limited in potential use, and he agreed with ICCVAM's recommendation. He described the Cell Transformation Assay based on the Bhas 42 cell line, which is used to evaluate carcinogenicity, noting that it can be used to replace animal testing. He supported the ICCVAM statement, which recommends its use, similar to the EURL ECVAM recommendation. Finally, he mentioned the 3T3 Neutral Red Update Cytotoxicity Assay, calling it a very useful test, noting that the ICCVAM and EURL ECVAM recommendations were similar. He said it was encouraging to see ICCVAM playing a more active role in international validation efforts.

Dr. Black, second discussant, said it was evident that ICCVAM and NICEATM have made a lot of progress over the past year. She said the profound hurdles presented by the fact that the end users of many of the assays are international corporations have become increasingly clear. She noted that the pharmaceutical industry had faced such an issue and created the ICH. But implementation of the 3Rs is not consistent in the international community generally. She recommended reaching out more proactively to regulatory agencies in countries such as China or Brazil, rather than waiting for them to come to ICATM. She suggested holding conferences in some of those countries to encourage their earlier and broader involvement. She also suggested coordinating, not just with the regulatory and governmental agencies, but looking for partnerships with other 3Rs organizations. Regarding ICCVAM's comments on EURL-ECVAM's recommendations, she related her impression that they concentrated on the limitations of the assays without discussing their positive aspects. She felt that there was no place to call for help with alternative approaches, and asked for end-user friendly documents providing guidance on the 3Rs, particularly materials about accepted alternative methods written in plain language.

Dr. Casey noted that Brazil is an observer to ICATM and would probably join ICATM next year. Regarding ICCVAM's responses to EURL-ECVAM recommendations, the use of the methods will inevitably be piecemeal. Thus, it is helpful for U.S. regulators to identify the shortcomings of the methods. He added that the other organizations beside EURL-ECVAM are also active, but that their processes do not translate as readily and sometimes their processes must go through OECD first.

Dr. Zuang recommended a document published by the OECD Hazard Assessment Task Force, which presents several relevant case studies and examples of how the alternative methods can be used.

Regarding the ICCVAM responses to the EURL-ECVAM recommendations, Dr. Willett said perhaps the issue is how they are presented, particularly the lack of discussion of positive potential uses of the methods. She recommended adding references to the OECD Guidances.

Dr. Khan noted that EURL-ECVAM recommendations include comprehensive reports on each test. Thus someone seeking more information could consult those reports, and he suggested they could be linked on the ICCVAM site.

VIII. Federal Agency Updates

A. Environmental Protection Agency

Dr. David Dix, Director of the EPA Office of Science Coordination and Policy in the Office of Chemical Safety and Pollution Prevention, provided an update on EPA's Endocrine Disruptor Screening Program (EDSP).

EDSP began in 1999, and has approached implementation through a series of chemical lists. List 1 evaluated 52 chemicals for estrogen, androgen, and thyroid interactions. Initial weight-of-evidence evaluations for the 52 chemicals are anticipated in December 2014. List 2 contains 107 chemicals, based on 41 pesticidal chemicals and 66 drinking water contaminants, and the Office of Management and Budget is reviewing the list for Tier 1 screening. Altogether there are 10,000 chemicals in the EDSP chemical universe.

Based on the current pace, it would take decades to screen all 10,000 chemicals, but recent advances in computational toxicology signal an important evolutionary turning point, fostering an accelerated pace of screening and testing, using predictive models to evaluate thousands of chemicals for potential risk to human health and the environment. Dr. Dix said this would overcome the throughput limitation of traditional toxicity testing. It would also allow replacement of some existing tests with non-animal alternatives. NICEATM has been working closely with EDSP over the past year, helping to translate the new tools into regulatory practice. The computational toxicology tools for screening and prioritization have included ToxCast and ExpoCast.

The EDSP universe of chemicals is being prioritized for EDSP screening using computational toxicology and other tools. Dr. Dix described completed and planned scientific advisory panel peer reviews. He said that EDSP Tier 2 test guidelines are currently undergoing revisions, with completion of test guideline documents expected by late 2014 or early 2015.

B. SACATM Discussion

Dr. Ochoa asked whether the EDSP plans to explore the interaction of endocrine disrupting chemicals (EDCs) in the environment, in terms of mixtures. Dr. Dix said the agency has a long-standing commitment to cumulative risk assessment. More specifically for EDCs, the issue has been addressed in concert with the Office of Research and Development, exploring non-monotonic dose response. A white paper on that topic was published last year and reviewed by the National Academy of Sciences; follow-up activities are being planned. Dr. Dix said approaches to cumulative risk assessment and chronic cumulative exposures will continue to be developed with a focus on endocrine pathways.

Dr. Lowit noted that it was important to remember that the EDSP is a screening program aimed at modernizing a testing strategy that uses many animals and takes a great deal of time and money. She said the decision to move from a testing strategy focused on screening prioritization to a regulatory program would be a separate series of discussions on the state of the science, adverse outcome pathways, overlap in the environment on the right biological scale, species of interest, and other factors. She noted that the focus is on modernizing the testing strategy, and that cumulative assessment is not necessarily on the horizon. Dr. Dix added that the screening program is currently focused on generating data sets for prioritization. Dr. Lowit said EPA is some distance from being able to do quantitative risk assessment on mixtures of endocrine disruptors. Dr. Ochoa said his concern was the potential for more than additive effects in mixtures, with some compounds potentiating each other. Dr. Dix said those questions are beyond the current scope of the EDSP.

C. Department of the Interior

Dr. Barnett Rattner, DOI, updated SACATM on alternative toxicology test method activities at the DOI, which has nine agencies and approximately 70,000 employees.

The DOI has limited regulatory authority on chemicals, mainly lying within the U.S. Geological Survey and the U.S. Fish and Wildlife Service. Those agencies conduct some toxicological research, mainly in the area of environmental contaminants. DOI regulatory authority includes registration of “shot” used in hunting of waterfowl and registration of some chemicals used in aquaculture. Dr. Rattner emphasized that DOI is committed to the 3Rs.

He also noted that DOI is involved with adverse outcome pathways (AOPs), particularly related to the effects of anticoagulant rodenticides, which can impact predatory birds when they feed upon poisoned rodents.

D. Food and Drug Administration

ICCVAM co-chair, Dr. Abigail Jacobs, briefed SACATM on current FDA-ICCVAM 3Rs-related activities.

She described activities at the Center for Drug Evaluation and Research (CDER). CDER participates in ICH guidance development, which reduces animal use in drug development. She described several initiatives for contributing to reduced animal use in toxicology testing, including acceptance of the 3T3 phototoxicity assay. Also, carcinogenicity studies have been waived for most biologics. CDER is considering an alternative battery to sometimes replace one species for regulatory use in reproductive toxicity tests. Dr. Jacobs noted that CDER has informed its constituents that there is no longer a need for a Draize test for skin or eye irritation.

CDER and ICCVAM are working together on several initiatives including a dermal sensitization non-animal battery, pathway-based assays, and ocular assays.

The Center for Biologics Evaluation and Research (CBER), which includes vaccines, cell therapy, and gene therapy, is continuing its leadership in efforts to replace the Murine Histamine Sensitization Test (HIST) for acellular pertussis vaccines. The group is also conducting ongoing research on non-animal approaches to potency testing for vaccines such as rabies, and will now accept non-animal endotoxin testing if it is appropriate for the product. Dr. Jacobs described other CBER activities related to cellular and gene therapies.

She also reported on 3Rs-related activities at the Center for Food Safety and Nutrition (CFSAN), which represents FDA on Tox21.

E. NIEHS

Dr. Nigel Walker, NIEHS/DNTP, updated SACATM on activities at NIEHS, noting that NICEATM is part of NIEHS and NTP. He described the *Toxicology in the 21st Century* origin of current efforts, including Tox21. Phase II of Tox21 was just completed, with the 10K library having been screened. Phase III, which focuses on tools for IVIVE, is just beginning. It also involves different cell systems, expanded utilization of lower organisms such as zebrafish and *C. elegans*, and a high throughput (HT) transcriptomics project.

Regarding implementation of alternative approaches, Dr. Walker discussed the NTP research response to the recent West Virginia chemical spill and work on aromatic phosphate flame retardants. This includes development of a battery of alternate models and test systems to screen for potential developmental neurotoxicity.

Describing new efforts at NTP in refining toxicology and testing methods, he provided details about the modified one-generation (MOG) study design that NTP has developed. It is designed to improve the ability to evaluate the impact of early-life exposures.

Addressing development of new alternative methods, he described several awards granted recently by the NIEHS SBIR/STTR programs that encourage development of new assays intended to reduce animal usage. He also discussed several collaborative activities being initiated within Tox21, where chemical sets are being distributed to investigators to interrogate to assess the utility of assays being developed.

F. Public Comment

Ms. Kristie Sullivan, representing PCRM, said, in general, PCRM supports the directions being pursued by the agencies and asked for more information on the MOG reproductive study design. She cited a similar effort by OECD, and wondered whether NIEHS had learned from that activity. Dr. Walker replied that the MOG is actually in response to what was perceived as some of the limitations of the OECD study design. He said it was felt that with a slight modification, better information across the whole of the life span would be generated. Ms. Sullivan asked if there would be opportunities for stakeholders to comment. Dr. Walker noted that the MOG was presented at the NTP Board of Scientific Counselors meeting last year for comment.

Ms. Sullivan said PCRM very much supports EPA's EDSP and the decision to apply computational toxicology to the EDSP. She also expressed support for NICEATM involvement in partnership with the EPA to find potential replacements of the current Tier 1 assays with *in vitro* methods. She noted the recent review publication by OECD of the currently available *in vitro* thyroid-related assays and suggested that NICEATM and EPA might use it as a guide in their efforts.

G. SACATM Discussion

Dr. Wilson summarized the discussion, stating that U.S. federal agencies have numerous examples of very practical implementation of alternatives. The agencies are staying abreast of changes and championing implementation of refined or alternative approaches.

XI. Updated ICCVAM Goals for FY2015

A. Presentation

Dr. Jacobs briefed SACATM on ICCVAM's goals for FY2015. There are three areas of priority: acute toxicity, skin sensitization, and AOPs. There will also be continued emphasis on international coordination and new paradigms for validation. She described several specific

goals in the area of acute toxicity testing, including participation in and formation of expert working groups.

Dr. Jacobs said skin sensitization testing is of interest to several agencies. Development of an integrated testing and decision strategy based on retrospective analysis of data from validated methods and Tox21/ToxCast data is among the priorities. She said the AOP approach is increasingly important and a goal is coordination of efforts across agencies in using AOPs for data sharing and communication. Another goal is development of an AOP for arsenic-related health effects, including lung cancer and ischemic heart disease.

ICCVAM will continue efforts toward implementing *in vitro* alternatives to the HIST for testing of acellular pertussis vaccines and exploring methods to reduce the number of hamsters used to create virulent test material for *Leptospira* vaccines. Dr. Jacobs concluded by stating that ICCVAM will work to increase international coordination initiatives and continue to develop and implement fit for purpose validation efforts.

B. SACATM Discussion

Dr. Ochoa voiced concern about how the activities described by Dr. Jacobs compare to activities that are not being done, how those decisions will be made, and what the alternative activities are. Dr. Jacobs said the selection of goals involves priorities and relatively short time spans. Dr. Casey said that after reorganizing two years ago, ICCVAM has just now returned to a full workload and going forward, tasks must be prioritized. Dr. Casey said that in terms of reducing animal use, there is no way to count rats and mice used in testing. He said people would be surprised to learn how many animals are being used in biologicals testing because they must be used for every batch being released. He agreed that testing should be put into the context of what is perceived as being the largest areas that could be impacted.

Dr. Janzen suggested that it might be more appropriate for ICCVAM to focus on one area where a validated method could be achieved. Dr. Casey agreed and noted that that approach is being taken in skin sensitization testing.

Dr. Black said she was unaware of a good reference for where the most animals are being used. Development of such a resource would help ICCVAM set its priorities. Dr. Zuang noted that there is a legal obligation in Europe to collect such information and it is published regularly.

Dr. Cavagnaro asked about the impact of the NIH policy to balance genders, and whether it is a policy or a requirement. Dr. Bucher said it is a policy. Dr. Jacobs said all of the studies received by her agency are balanced by gender. Dr. Black cited a recent magazine editorial contesting the need for gender balance in studies, in that it may result in unnecessary duplication of efforts and excessive use of animals, in some cases doubling use.

X. Report on Meetings

A. Aquatic Models and 21st Century Toxicology

Dr. Jon Hamm, ILS-NICEATM, reported on the Collaborative Workshop on Aquatic Models and 21st Century Toxicology, which was held May 5-6, 2014, at North Carolina State University (NCSU) and co-sponsored by NCSU and NIEHS. It attracted nearly 150 participants from the U.S., Canada, Europe, and Asia. Following an opening session on the regulatory perspective on the use of aquatic vertebrate models, plenary sessions covered: cardiovascular toxicology, developmental processes in toxicology and disease, emerging technologies, models of neurobehavior and neurotoxicology, predicting alterations to the immune system, and emerging issues. A workshop summary report will be published in the peer-reviewed literature and discussions are underway for follow-up workshops. Dr. Hamm noted that collaborations with researchers employing aquatic vertebrate species ensued from the meeting.

B. ICCVAM/NICEATM Workshop on Alternatives to the HIST for Acellular Pertussis Vaccines

Dr. Richard McFarland, FDA/CBER, briefed SACATM on a satellite meeting to World Congress 9 in Prague, Czech Republic, held August 24, 2014, that was co-sponsored by ICCVAM and NICEATM. This workshop focused on discussions related to the development and implementation of *in vitro* assays to replace the murine HIST test for acellular pertussis vaccines. Specific issues discussed included the relation of alternatives with a consistent approach in manufacturing, the necessary framework for regulatory acceptance of a harmonized alternative approach to HIST. Dr. McFarland described the current status of the international collaborative study assessing use of the Chinese Hamster Ovary (CHO) cell assay, the results of which are anticipated in early 2015. These results will be the focus of the next meeting of the international alternatives of HIST working group on March 4-5, 2015, in London, England, which is co-sponsored by ICCVAM and NICEATM.

Dr. Black asked why a specific ELISA to the toxoids could not be developed. Dr. McFarland explained a specific ELISA alone would not be sufficient to meet the needs of the test to residual active pertussis assay in vaccine product.

Dr. Willett asked if any other cell lines had been tried in developing an alternative to the HIST. Dr. McFarland replied that although cell lines might prove as a potential sources for an alternative test, at this time the historical data with CHO in pertussis vaccine testing regimen, including known ability to identify toxin enzymatic activity, made CHO cells the reasonable choice. He said if the CHO cell test effort were successful, an obvious next step would be to develop a cell line-sourced assay. Dr. Ochoa praised the makeup of the committee, with representatives from academia, industry, and government. He felt that the mix was important.

Dr. Cavagnaro asked if the representatives from industry are scientific experts or regulatory affairs people. Dr. McFarland said that most of those individuals have experience in both areas and all have experience with the HIST. Dr. Cavagnaro pointed out that in industry there are scientists and there are regulatory experts, and they don't always agree. Dr. McFarland said he had seen that dynamic in other activities, but that this had not been a problem with the CHO cell alternative to the murine HIST test.

Dr. Regimbald-Krnel said the HIST is very difficult, and has many issues from a regulatory standpoint, which is helping to push the need to find a replacement test.

C. Adverse Outcome Pathways

Dr. Nicole Kleinstreuer, ILS-NICEATM, reported on the workshop held September 3-5, 2014, at the NIH Natcher Conference Center in Bethesda, titled *Adverse Outcome Pathways: From Research to Regulation.* The AOP workshop was co-sponsored by NICEATM and PCRM, with 120 people attending in person along with another 350 people viewing by webcast. The meeting consisted of symposium talks, discussion forums, poster sessions, junior investigator awards, hands-on demonstrations, and rotating breakout groups. Dr. Kleinstreuer described the conclusions reached by the breakout groups and follow-up activities including the formation of an AOP email listserv that NICEATM will manage. She summarized the key messages from the workshop as involving people, process, priorities, and partnering.

Dr. Wilson asked about discussion at the workshop of the role of SNPs in AOPs. Dr. Kleinstreuer said there was virtually no discussion of that topic at the workshop. She said that genetic variability is a wide-open topic that needs to be discussed.

D. SACATM Discussion

Dr. Willett, lead discussant, who attended the Aquatic Models workshop as the SACATM representative, reported on her impressions of the meeting. She said there had been terrific progress in the technology over the past eight years, which was on full display at the workshop. She said incorporation and application of pathway-based approaches could be very helpful, but was still underutilized in aquatic toxicology. The workshop was successful in bringing pathway-based ideas to the aquatic toxicology community. She summarized the main points of the workshop, one of which was to explore how the aquatic toxicological models, which have been in common use in drug development, could be used more broadly in human health risk assessment. She said in the future, careful measurement of the ADME properties of zebrafish would be needed, as well as improved image analysis and higher throughput assays.

Dr. Cavagnaro asked about extrapolations from compound concentrations used in zebrafish screening to *in vivo* dosing. Dr. Kleinstreuer described a number of current, parallel projects

working to address that question. Dr. Wilson noted that another approach to dosimetry is to use the Globally Harmonized System criteria.

Dr. Cavagnaro, SACATM representative at the AOP workshop, said she was impressed by the mix of attendees although surprised that more were not in attendance from the pharmaceutical industry. She praised the many opportunities for dialogue and interaction among attendees. She described her perceptions of the key messages imparted at the workshop. She said it would be critical to provide justification for the use of alternative tests in order to encourage acceptance at the regulatory level, and the opportunity for interaction between industry and regulators is helpful in that regard.

Dr. Black expressed interest in how much the fish might potentially be a predecessor to reduce later animal use, as at least a non-mammalian screening step. She was glad to hear that pharmacokinetic work is advancing in the fish. She asked if EPA had established pre-filing opportunities for dialogue about opportunities to reduce animal use through non-mammalian models. Dr. Lowit said that those dialogues are already taking place, in pre-registration meetings.

Dr. Ochoa addressed Dr. Cavagnaro's comment about the lack of participation in the AOP workshop by pharmaceutical industry representatives. He said that perhaps there was low pharmaceutical industry participation because the whole AOP concept needs to be developed further for acceptance by pharmaceutical toxicology groups.

Closing the meeting, Dr. Wilson commented about the overall enthusiasm and interest expressed by SACATM at the meeting for NICEATM's and ICCVAM's activities. He adjourned the SACATM meeting at 5:30 PM, September 16, 2014.