

**Summary Minutes**

**Scientific Advisory Committee on  
Alternative Toxicological Methods Meeting  
September 18-19, 2017  
National Institutes of Health, Bethesda, MD**

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## II. Location of Background Materials and Presentations

Background materials and presentations for the 2017 SACATM meeting are available on the SACATM meeting website (<https://ntp.niehs.nih.gov/go/8202>).

## III. Frequently Used Abbreviations

|                    |  |
|--------------------|--|
| 3Rs                | replacement, reduction, or refinement (causing less pain and distress) in the use of animals for toxicological testing |
| ACC                | American Chemistry Council   |
| AOP                | adverse outcome pathway  |
| CPSC               | Consumer Product Safety Commission   |
| DoD                | Department of Defense  |
| EPA                | Environmental Protection Agency  |
| FAIR               | findable, accessible, interoperable, and reusable (data sharing principles)  |
| FDA                | Food and Drug Administration   |
| GSK                | GlaxoSmithKline  |
| HESI               | Health and Environmental Sciences Institute  |
| HSUS               | Humane Society of the United States  |
| IATA               | integrated approaches for testing and assessment   |
| ICATM              | International Cooperation on Alternative Test Methods  |
| ICCVAM<br>Methods  | Interagency Coordinating Committee on the Validation of Alternative<br>Methods   |
| ICE                | Integrated Chemical Environment  |
| ILS                | Integrated Laboratory Systems, Inc.  |
| IVIVE              | in vitro to in vivo extrapolation  |
| LCSA               | Lautenberg Chemical Safety Act   |
| LLNA               | murine local lymph node assay  |
| MAD                | Mutual Acceptance of Data (OECD)   |
| NA3RsC             | North American 3Rs Collaborative   |
| NAMs               | new approach methodologies   |
| NCATS              | National Center for Advancing Translational Sciences (NIH)   |
| NCCT               | National Center for Computational Toxicology (EPA)   |
| NGO                | nongovernmental organization   |
| NICEATM<br>Methods | NTP Interagency Center for the Evaluation of Alternative Toxicological<br>Methods                                      |
| NIEHS              | National Institute of Environmental Health Sciences (NIH)  |
| NIH                | National Institutes of Health  |
| NIST               | National Institute of Standards and Technology   |
| NTP                | National Toxicology Program  |
| OECD               | Organisation for Economic Co-operation and Development   |
| OPP                | Office of Pesticide Programs (EPA)   |
| OPPT               | Office of Pollution Prevention and Toxics (EPA)  |
| PCRM               | Physicians Committee for Responsible Medicine  |
| PETA               | People for the Ethical Treatment of Animals  |
| QSAR               | quantitative structure-activity relationship   |
| RFA                | Request for Application  |

|        |  |
|--------|--|
| SACATM | Scientific Advisory Committee on Alternative Toxicological Methods |
| SBIR   | Small Business Innovation Research                                 |
| STTR   | Small Business Technology Transfer                                 |
| SSWG   | Skin Sensitization Working Group (ICCVAM)                          |
| TSCA   | Toxic Substances Control Act                                       |

#### IV. Attendance

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on September 18 and 19, 2017, at the National Institutes of Health (NIH) in Bethesda, Maryland. The following individuals attended the meeting:

##### Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) Members

Brian Berridge, DVM, PhD, DACVP, GlaxoSmithKline (GSK)  
Michael Bolger, PhD, Simulations Plus, Inc.  
Kelly Coleman, PhD, DABT, RAC, Medtronic PLC  
Hisham Hamadeh, PhD, DABT, MBA, Amgen, Inc.  
William Janzen, Epizyme, Inc. (chair)  
Lawrence Milchak, PhD, DABT, 3M  
Pamela Spencer, PhD, DABT, ANGUS Chemical Company  
Catherine Willett, PhD, The Humane Society of the United States (HSUS)  
ClarLynda Williams-Devane, PhD, North Carolina Central University  
Wei Xu, PhD, University of Wisconsin at Madison  
Hao Zhu, PhD, Rutgers University

##### Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Principal Representatives

Surender Ahir, PhD, Occupational Safety and Health Administration  
John Elliott, PhD, National Institute of Standards and Technology  
Bert Hakkinen, PhD, National Library of Medicine  
Steve Hwang, PhD., Department of Transportation  
Abigail Jacobs, PhD, Food and Drug Administration (FDA), ICCVAM Co-chair  
Ron Johnson, PhD, National Cancer Institute  
Anna Lowit, PhD, U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP), ICCVAM Co-chair  
Joanna Matheson, PhD, Consumer Product Safety Commission (CPSC)  
Moiz Mumtaz, PhD, Agency for Toxic Substances and Disease Registry

##### Other ICCVAM Representatives

LTC Marla Brunell, Department of Defense (DoD)  
Jeanne Goshorn, National Library of Medicine  
Donna Mendrick, PhD, FDA  
Mark Miller, PhD, National Cancer Institute  
Arianne Motter, PhD, FDA  
Elijah Petersen, PhD, National Institute of Standards and Technology

Emily Reinke, PhD, DoD

Louis (Gino) Scarano, PhD, EPA Office of Pollution Prevention and Toxics (OPPT)

## **International Cooperation on Alternative Test Methods (ICATM) Representatives**

Charu Chandrasekara, Canadian Centre for the Validation of Alternative Methods

Tae Sung Kim, Korean Center for Validation of Alternative Methods

## **National Institute of Environmental Health Sciences (NIEHS) Staff**

Linda Birnbaum, PhD, DABT, ATS

John Bucher, PhD, DABT

Warren Casey, PhD, DABT

Robbin Guy

Nicole Kleinstreuer, PhD

Elizabeth Maull, PhD

Daniel Shaughnessy, PhD

Mary Wolfe, PhD

## Integrated Laboratory Systems, Inc. (ILS, NICEATM support contractor) Staff

David Allen, PhD  
Steven Morefield, MD  
Catherine Sprankle  
June Mader (subcontractor, GOFORWARD LLC)

## Public

Richard Becker, PhD, American Chemistry Council (ACC)  
Amy Clippinger, PhD, People for the Ethical Treatment of Animals (PETA)  
Christine Colvis, National Center for Advancing Translational Sciences (NCATS)  
Jennifer Goode, FDA  
Katherine Groff, PETA  
Esther Haugabrooks, PhD, Physicians Committee for Responsible Medicine (PCRM)  
Erin Hill, Institute for In Vitro Sciences  
Tina Hilton, PETA  
Mark Johnson, PhD, DABT, ATS, DoD  
Vicki Katrinak, HSUS (by phone)  
Tim McMahon, PhD, EPA OPP  
Geoff Patton, PhD, FDA  
Norman Peterson, North American 3Rs Collaborative (NA3RsC)  
Pat Rizzuto, Bloomberg BNA, Inc.  
Craig Rowlands, PhD, Underwriters Laboratories  
Tinashe Ruwona, PhD, Institute for In Vitro Sciences  
Seema Schappelle, PhD, EPA  
Regina Sheffield-Wright, NHLBI  
Kristie Sullivan, MPH, PCRM  
Rusty Thomas, PhD, EPA National Center for Computational Toxicology (NCCT)  
Douglas Wolf, PhD, Syngenta Crop Protection

## September 18, 2017

### V. Welcome and Opening Remarks

SACATM met on September 18 and 19, 2017, at NIH in Bethesda, Maryland. Mr. William Janzen, SACATM chair, called the meeting to order at 9:00 a.m. on September 18. Attendees introduced themselves, and Mr. Janzen welcomed the new SACATM members: Drs. Michael Bolger, Kelly Coleman, and ClarLynda Williams-Devane. In her welcoming remarks, Dr. Linda Birnbaum, NIEHS and National Toxicology Program (NTP) Director, commented on the progress made towards reducing animal use in testing since ICCVAM's 2013 reinvention, which shifted control and direction of ICCVAM's activities to the member agencies. Examples of this progress include the Environmental Protection Agency (EPA) guidance for test waivers, and EPA's application of high throughput screening methods and associated computational models to the testing requirements of the Endocrine Disruptor Screening Program. Dr. Birnbaum also noted the efforts of the ICCVAM Skin Sensitization Workgroup in

developing multiple machine-learning approaches to predict skin sensitization hazard; interagency collaboration being central to this effort. The roadmap scheduled for discussion at this meeting was developed through a process that involved almost 90 ICCVAM agency scientists and provides a framework to accelerate development of new methods. She noted that comments made during this meeting, as well as comments from previous public meetings, would be considered as the plan is finalized.

Dr. Birnbaum concluded her remarks by noting the official addition of the National Institute of Standards and Technology (NIST) to ICCVAM. She acknowledged the attendance of Drs. Tae Sung Kim and Charu Chandrasekara, representing the Korean Center for Validation of Alternative Methods and the Canadian Centre for the Validation of Alternative Methods, respectively. Dr. Birnbaum recognized Dr. Abigail Jacobs on her upcoming retirement from the Food and Drug Administration (FDA) and thanked her for her years of service to ICCVAM, most recently as ICCVAM Co-chair. Dr. Birnbaum also recognized and thanked retiring SACATM members Mr. Janzen and Drs. Catherine Willett and Wei Xu for their service.

Dr. Mary Wolfe, the SACATM Designated Federal Official, read the conflict of interest statement and reviewed meeting logistics. ICCVAM Co-chairs Dr. Anna Lowit and Dr. Jacobs each made brief welcoming remarks.

## VI. Overview of U.S. Strategic Roadmap

Dr. Warren Casey, Director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), presented an overview of the strategic roadmap to guide development of new approaches to evaluate the safety of chemicals and medical products in the United States. The traditional U.S. process for alternative method validation fails to provide methods that are useful to regulators. The goal of the roadmap is to overcome this deficiency by facilitating a process that produces useful methods with stakeholder involvement. Through a review of ICCVAM agency strategic plans and a February 2017 meeting of ICCVAM agency scientists, three common themes emerged: communication, collaboration, and commitment. The roadmap distinguishes itself from the ICCVAM Authorization Act of 2000 by identifying agency efforts to realize the requirements set out by the Act. The proposed roadmap expands consideration beyond chemicals to include medical products, focusing on human health and relevance rather than ethical consideration of animal use in safety testing, and developing implementation plans for each identified activity. The roadmap is scheduled to be published by the end of 2017.

**Clarifying questions and comments:** In response to a question posed by Dr. Coleman, Dr. Casey said that international and ICCVAM activities are coordinated through participation of ICATM representatives on ICCVAM workgroups and in other cooperative activities. Dr. Willett asked if the implementation plans would be agency- or office-specific; Dr. Casey thought that, while the goal of the roadmap is to be broader than that, an effort would be made to provide agency-specific context of use.

## Public Comments

Four written public comments were submitted for this section, on behalf of People for the Ethical Treatment of Animals (PETA), Syngenta Crop Protection LLC, North American 3Rs Collaborative (NA3RsC), and Humane Society of the United States (HSUS).<sup>1</sup>

### **Oral Public Comments**

Dr. Richard Becker, representing the American Chemistry Council (ACC), suggested that the roadmap include adoption and implementation of a framework for establishing scientific confidence. ACC has adapted an Institute of Medicine approach that includes assay performance assessment through analytical validation, assay data interpretation and inference qualification for specific intended purposes, and transparent justification supporting assay use within a specific decision context. Dr. Becker provided examples of how this approach has been applied.

Ms. Vicki Katrinak<sup>2</sup>, representing HSUS, communicated that human data should be the benchmark for alternative methods development; establishing confidence in new approach methodologies (NAMs) relies on in vivo animal data that often fail to predict human responses. In the absence of human data, parallel data collection from animals should be permitted with the intention of phasing out animal data collection over time. An example of a relevant approach is the 2016 Health and Environmental Sciences Institute (HESI) criteria for evaluating reliability and predictivity of new non-animal methods. While HSUS strongly supports ICCVAM's review of animal data variability, it remains critical to continue to evaluate how well animal data reflect human outcomes. As part of the effort to determine information needs, HSUS encourages agency review of the legal requirements for animal data; identification of legal requirements for specific tests could inform the activities likely to have the greatest impact. Regulations and laws should be updated to accommodate changes in technology, such as the use of the term "information" rather than "data" in the Lautenberg Chemical Safety Act (LCSA).

Dr. Norman Peterson, representing NA3RsC, introduced the International Consortium for Innovation and Quality in Pharmaceutical Development, which includes a 3Rs leadership group. Specific areas of interest include physiological systems, as well as reproducibility, endpoints, and technology in animal care. Dr. Peterson then focused his remarks to refinement, collaboration, and communication in the context of supporting 3Rs activities in research and testing. The current trend in refinement is focused on biomarkers, behavior, and physiology rather than terminal endpoints, clinical pathology, and limited physiologic parameters, using, for example, imaging technologies for refinement. NA3RsC is developing a central resource and conduit for communicating 3Rs concepts with industry and government entities. The organization's website and Virtual 3Rs Collaborative includes resources such as poster presentations, webinars, and commercial resources. Dr. Casey noted this organization could be a good resource for facilitating the public-private collaborations that are going to be key to roadmap success.

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<sup>1</sup> Written public comments for all topics are available at <https://ntp.niehs.nih.gov/go/8202>.

<sup>2</sup> Ms. Katrinak delivered her comments by telephone.



***Comments from Designated SACATM Discussants***

Dr. Brian Berridge, first discussant, commented that the roadmap is starting to focus on areas where there have been gaps in the past. Rather than focusing on the technology alone, there is a need to identify specific problems and then determine how to apply the technology to address the problem. While the various stakeholder groups have different decision-making drivers, commonalities exist that could be taken advantage of to move forward. It will be important to leverage the available industry information and data, most of which are generated in the pre-regulatory arena. Industry needs to be more forthcoming with their data and experience to help build confidence in new methods. Dr. Casey agreed that access to data is important, as is an analytic infrastructure. How to develop that infrastructure needs to be discussed.

Dr. Hisham Hamadeh, second discussant, noted the need to articulate problems before advancing solutions, even before the technology is available. Agencies need to clearly and consistently define their data requirements. Connecting end-users with developers is very important; ICCVAM can help prioritize needs and moderate discussions among these entities. Confidence in new technologies comes through experience and time, but communicating industry experience with new methods could accelerate confidence-building in valuable new technologies. Technologies that fail to address useful problems need to be identified and set aside. Federal agencies could provide a means for communicating method successes and failures. Finally, ICCVAM needs to consider how new technologies for collecting human data can be exploited; these technologies could yield critical data that complement screening technologies. An expanded universe of stakeholders could increase the availability of different types of real-world data for application to new methods development. Dr. Casey added that the markets influence what goes forward; method developers need to provide a product that addresses a specific problem. Drs. Birnbaum and Janzen appreciated Dr. Hamadeh's attention to the question of variability in human population, which has yet to be modeled well by either animal or in vitro studies.

Dr. Willett, third discussant, reiterated the importance of identifying agencies' information needs; the scoping exercise suggested by HSUS would capture the legislative requirements, the agencies' interpretation of those requirements, and other information needs.

Dr. Hao Zhu, fourth discussant, noted that, while important advancements have come from industry and federal programs like ToxCast, academia has the potential to make important advances with appropriate funding and information. Initiatives to promote research to predict animal toxicity would be helpful. Dr. Birnbaum responded that NIEHS' small business grants are available to support novel test systems, and the amount of funding for them is increasing.

***Additional SACATM Comments***

There was a general positive response to the roadmap.

Dr. Pamela Spencer noted the list of potential collaborators should be expanded beyond federal agencies to include state partners.

Dr. Williams-Devane was glad to see the limitations of a linear validation process and

operating in silos recognized. ICCVAM needs to consider development of a standardized vocabulary, be conscious of the process for establishing data quality standards, and the variability of these standards among different areas. Dr. Casey noted that standardized ontologies are particularly important in discussions of adverse outcome pathways (AOPs); Dr. Bucher added that standardized vocabularies are also important for systematic review.

Dr. Laurence Milchak emphasized the importance of maintaining an international perspective. Industry is hesitant to adopt new methods for fear that they might not adequately protect human health. Better communication of success stories would be useful. Dr. Casey agreed with the importance of international harmonization and the need to highlight accomplishments of, for example, the European Union Reference Laboratory for Alternatives to Animal Testing, when appropriate.

Dr. Xu noted the importance of in vitro assay reproducibility among different laboratories. Potential new assays users, including industry, need to participate in their validation. She also noted that molecular profiling could be a useful technology for refinement. Validation of new assays will ultimately require human data; pharmacogenomic data might be useful for validation, but the data needs to be made available and utilized earlier in the validation process.

## VII. Strategic Goal: Encourage Adoption and Use of New Approaches by Federal Agencies and Regulated Industries

Dr. Lowit introduced this section by stating that new methods development should be a collaborative effort between industry and regulatory agencies, both domestically and internationally. Industry will only conduct globally accepted tests. She said the Syngenta case study demonstrates how regulators and industry can work together to identify goals and the data needed to achieve the goal. The Syngenta approach can help to build confidence in new methods by both regulators and industry.

### Presentation: Implementation of RISK21

Dr. Doug Wolf, Syngenta Crop Protection, introduced his topic by noting that Syngenta's goal is to do the right testing, at the right time, for the right reason, in both discovery and reregistration processes. This includes not only testing for human health endpoints but also for ecological risk assessment. Syngenta's approach to achieving this goal is to move away from hazard identification and towards an integrated evaluation strategy to identify the context in which a chemical causes an adverse effect and appropriate risk management steps to prevent these adverse effects. Syngenta participates in RISK21<sup>3</sup>, a HESI-managed initiative with participants from government, industry, academia, and nongovernmental organizations (NGOs) to support process development for the integrated evaluation strategy. The RISK21 paradigm begins with problem formulation, exposure assessment, and toxicity identification; finally, toxicity is considered in the context of the exposure. These evaluations can identify areas for additional resource

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<sup>3</sup> <http://risk21.org/>

allocation, for example, towards exposure characterization when that data is more limited. Dr. Wolf presented three examples of this approach where the missing information focused on (1) exposure assessment, especially in the case of potential misuse; (2) environmental questions including product use in aerial and ground spraying; and (3) inhalation toxicity. Dr. Wolf cited EPA waivers as examples of how building on what is already known can help avoid unnecessary testing. The envisioned outcome of these efforts is “a globally harmonized science-based approach centered on a risk assessment and management paradigm for decision-making that results in the elimination of studies not relevant or used for human health risk assessment.”

**Clarifying questions and comments:** In response to a question posed by Dr. Bolger, Dr. Wolf said that within the context of use exposure considers the amount used, the route of likely exposure, and the mechanism of toxicity in the species of interest. The context of use can help put boundaries on the questions to ask. Dr. Bolger commented that in vitro to in vivo extrapolation (IVIVE) methods used in these exposure models can be difficult to apply if there are no preclinical data. Dr. Wolf agreed, noting that a major area of concern by the HESI workgroup was the lack of information about exposure.

## Public Comments

Three written public comments were submitted for this section on behalf of PETA, NA3RsC, and the Center for Responsible Science.

### **Oral Public Comments**

Ms. Kristie Sullivan, representing Physicians Committee for Responsible Medicine (PCRM), encouraged individual agencies to develop statements indicating their commitment to alternative methods; these statements should be as specific as possible. Agency statements, like the EPA Office of Pesticide Program (OPP) 2016 letter to stakeholders, indicating their openness to new approaches and invitations to collaborate alert industry to existing opportunities. Statements posted on an agency’s website are more useful than presentations made at conferences. Likewise, the regulated industries have a responsibility to participate and bring forward useful data and technologies. International cooperation remains a continuing area of concern. Recently the Organisation for Economic Co-operation and Development (OECD) moved towards applying new methods more rapidly, but this is dependent on membership participation and efforts. Participation needs to be broad to ensure that the emerging guidance is widely applicable.

Ms. Katherine Groff, representing PETA, praised OPP for making information about acceptable new methods and approaches available on their website, and encouraged other agencies to adopt EPA’s approach. She urged agencies to expedite the review of submissions that include non-animal data, perhaps as an incentive to adopt alternative methods. Ms. Groff recommended the use of a quantitative tracking system to monitor acceptance rates of non-animal versus animal tests to help identify barriers to acceptance. She recognized the ICATM skin sensitization workshop as an example of activities that could help accomplish global regulatory acceptance and encouraged SACATM support of similar activities. Dr. Casey noted that the United States plans to

host another ICATM conference on establishing confidence in new methods next year. He also commented that it is important to include the needs of the non-regulatory agencies who may have more flexibility to adopt new methods.

Both Ms. Sullivan and Ms. Groff noted the importance of training and said PCRM and PETA are willing to collaborate with relevant stakeholders to facilitate this training. Ms. Groff specifically noted that PETA has experience in organizing workshops and assembling resources.

### ***Ad Hoc Comments from Public***

Dr. Peterson, NA3RsC, noted that the roadmap needs to consider the educational avenues that can be used for training.

Dr. Becker, ACC, commented that the roadmap could be strengthened by integrating exposure into risk assessment. Dr. Lowit agreed that using available exposure and mechanistic knowledge will help determine research needs. Dr. Becker suggested that this could be accomplished through a tiered exposure evaluation. Dr. Casey commented that that is important from both a scientific and an animal use standpoint; using a hazard-based rather than a risk-based paradigm tends to drive animal use. Dr. Becker commented that understanding that a data gap is not necessarily a data need will help move us away from a checkbox-type approach to data generation.

### ***Comments from Designated SACATM Discussants***

Dr. Coleman, first discussant, described the evolution of international standards for medical device testing, in which a checklist of animal tests has yielded to a testing matrix that begins with chemical characterization and risk assessment before conducting animal tests. FDA recently finalized a fast-track expert review process for new methods' evaluations for medical devices<sup>4</sup>. Medtronic is considering replacing the traditional rabbit test for skin irritation testing with in vitro human skin models. A study of these models is expected to be published soon in a special edition of *Toxicology In Vitro*; it is anticipated that this study will become the basis for a new standard for in vitro irritation testing of medical devices. Data from these models will be submitted to FDA through their expert review program. Medtronic hopes FDA will provide specific guidance about what data they need, with examples of successful submissions and methods that were used.

Dr. Hamadeh, second discussant, noted that the comfort people have with traditional approaches presents a challenge for the implementation of new approaches. To overcome this, companies need unambiguous communication from agencies about what information is needed. Lack of international harmonization is also a challenge: a major country regulation can become a common denominator for regulated industry. Agencies need to communicate what their vision for replacing animal tests might look like as frequently updated, living documents. Industries in turn have a responsibility to bring forward data that will be useful for this effort.

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<sup>4</sup> Announced in Federal Register, August 10, 2017; <https://www.federalregister.gov/d/2017-16827>. Information about the FDA Medical Device Development Tools program is available at <https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm>.

Dr. Milchak, third discussant, commented that there is currently a lack of available alternatives for all endpoints of interest. Many 3M chemicals of interest have properties that make it challenging to apply alternative methods; 3M would like to work with agencies to develop methods that would be useful in these situations. New method development incentives would be very useful, as would publicizing successes.

Dr. Spencer, fourth discussant, emphasized the importance of considering exposure in deciding which tests are needed to answer relevant questions, especially for consumer products. Interested parties need to have an informal collaboration mechanism to foster development and build confidence in alternative methods. Supporting these collaborations is the most important thing that agencies can do. Dr. Casey asked Dr. Spencer what she perceived were the barriers to such collaboration. Dr. Spencer replied that the most important needs are (1) funding and (2) a home for the collaboration mechanism. This is an area where public-private partnership will be important.

### ***Additional SACATM Comments***

Dr. Willett noted that ICCVAM needs to identify or nurture the right agency people, at both the leadership and grassroots levels, to move these initiatives forward. It is important to understand the regulatory drivers and goals of individual agencies and even within different programs within a single agency. Similarly, international harmonization represents a significant challenge. The OECD Mutual Acceptance of Data (MAD) agreement does not guarantee that data will be accepted everywhere. Integrated approaches to testing and assessment (IATA) may be an effective way to use non-animal methods, especially considering the different capabilities and technologies available to individual countries. Dr. Lowit asked if OECD planned to extend the application of MAD to IATA, as they have done with defined approaches. Dr. Willett responded that OECD does not plan to extend MAD to IATA; however, countries will have the flexibility to adopt the defined approach that works best for their needs.

Dr. Casey agreed that identifying the right people within agencies is key, especially those that are truly interested. He also noted that OECD test guidelines tend to be validated for a very limited chemical space; helping to expand that chemical space will help to meet the needs of the agencies.

Dr. Bucher, NTP Associate Director, encouraged SACATM members and industry representatives to consider the best means through which agency interaction could take place. This might include creating safe harbors. Dr. Wolf responded that he thought there were some opportunities already in place. He noted that Syngenta's alternative inhalation approach will be going to an EPA federal advisory committee for review next year. Many regulatory agencies are open to identifying opportunities to work within their current processes to develop new methods and develop confidence in them. Dr. Spencer asked how other companies adopt new approaches. Dr. Wolf indicated that technology transfer occurs through public meetings and publications. Dr. Lowit added that innovative approaches developed within regulated companies need to be identified and applied more broadly to relevant problems; working together on a broader scale will help that happen. Dr. Bucher asked what would be the best way to determine when innovative technologies are broadly applicable. Dr. Lowit thought that more clearly articulated agency concerns would be helpful; for example, when good animal models

are lacking, agencies should indicate the specific health outcome(s) they are interested in.

Mr. Janzen commented that in product development, testing turnaround time is very important; demonstrating a correlation between data obtained through other more efficient methods and in vivo test data is key to reducing these times. Sharing these correlations with regulatory agencies could help speed late-stage development. Dr. Milchak agreed and noted that an expedited review process would be an incentive for the use of alternative methods, as would agency recognition of a successful validation effort by a company. Dr. Jacobs responded that agencies are restricted from promoting commercial entities. She also noted that companies are reluctant to share information that gives others a commercial advantage. Dr. Hamadeh noted that FDA recognized the innovation of one of the companies at the forefront of digital prescriptions without mentioning the specific company. Dr. Casey indicated that, if it is problematic for agencies to provide recognition, ICCVAM can do so.

Dr. Bucher noted that the Open Data Act, proposed federal legislation attached to the defense authorization bill, addresses the availability of data that the federal government uses to make decisions.

## VIII. How Will ICCVAM Measure the Strategic Roadmap's Success?

Dr. Casey introduced this topic by stressing its importance and noting that ICCVAM is seeking SACATM's input on this topic. Developing publicly accessible and transparent measures to gauge success is a challenge in the United States. The recently proposed FACT Act would require animal numbers and use information be added to the ICCVAM Biennial Report. While sounding straightforward, in fact, this would create a considerable burden to agencies. The Animal Welfare Act specifically excludes rats, mice, and birds from the Department of Agriculture's reporting requirements. The Public Health Service Policy on Humane Care and Use of Laboratory Animals only covers those entities funded by the them, and only requires reporting of an average daily facility census, with no information collected on animals use. Neither the Act nor the Policy obtains data useful for determining the number of animals used in testing or the types of tests used. Because of these limitations, the United States is unable to compile the same information that is available, for example, in Europe. In addition, reporting requirements vary widely by agency; therefore, the ability to extract animal use data also varies. Some agencies lack any requirement for routine data collection or data collection related to product failures. Lack of international harmonization will continue to drive animal testing even if U.S. agencies could track animal use. Tracking numbers of validated methods is unsatisfactory as validation of a new method does not guarantee its use. One approach to addressing this problem is to track waivers and estimated animal savings. Meaningful opportunities to use animal numbers should be used when possible. For example, the Department of Agriculture can track animal use for leptospirosis tests. A second approach would target specific applications for eliminating animal use, such as biologics testing. Standardized electronic reporting could also facilitate use of data analytics to identify success stories and areas for increased resource investment.

**Clarifying questions and comments:** In response to a question posed by Dr. Bolger, Dr. Casey replied that, while not wanting to share specific information on animal numbers, animal vendors are interested in working with ICCVAM to address this issue. Responding to Dr. Spencer's question on "standardized electronic reporting," Dr. Casey indicated that the same information that is currently reported would be put into a standardized electronic format to facilitate location of specific data by the end-user.

## Public Comments

One written public comment was submitted for this section on behalf of PETA.

### **Oral Public Comments**

Ms. Sullivan, representing PCRM, noted that, in order to measure success, it is generally agreed that setting goals and determining how to meet them is important. We need additional data to determine our success in replacing animals used in testing. These activities should be seen as a targeting strategy. She cited animal use in pyrogen testing in Europe as an example of how data can identify gaps in implementation. A baseline is needed to know where we are starting from and to identify areas for increased investment. Collaborations will be important to this effort. In closing, Ms. Sullivan encouraged the agencies to consider how baselines could be set and how to communicate their visions for success. Dr. Casey suggested that using data from other countries and estimating the numbers of animals used per test or activity are potentially useful activities that would be more productive than spending the resources needed to count animals.

### **Ad Hoc Comments from Public**

Dr. Wolf asked what would incentivize lab animal suppliers to help with this effort. Dr. Casey indicated that some of these companies are currently engaged in this area. Dr. Berridge added that contract research organizations have economic reasons to be interested in moving away from animal use and towards platforms like microphysiological systems.

### **Comments from Designated SACATM Discussants**

Dr. Berridge, first discussant, noted that GlaxoSmithKline (GSK) counts animal numbers and reports year-to-year changes. GSK once had a goal simply of reducing animal use; this has evolved to focus more on human relevance and increasing efficiency. While there is a danger in simply counting assays, incentivizing assay development will facilitate the validation and use of good assays. The key is to link specific platforms to regulatory needs and build confidence in the new methods to the point that companies are comfortable moving away from animal testing.

Dr. Willett, second discussant, commented that metrics are important for prioritization, to measure progress, and to identify implementation gaps. An example of this is the Corrositex method. After initial validation, Corrositex failed to be widely used because it had a narrow applicability domain. This problem was addressed only after recognizing that animal tests were still conducted in the area for which its application was appropriate. Dr. Willett recognized that it is difficult for agencies to measure progress without legal requirements for data or reporting; however, there are examples of things

that can be done, including counting waivers and bridging and formatting electronic data submissions to include information on specific data requirements satisfied by in vitro data. Regulatory agencies could also publicize examples of alternative usage with realized animal savings, or focus on the costs of animal versus non-animal testing. While agencies are limited in the kind of information that they can divulge, perhaps companies could consider sharing their data. Progress in reducing animal use in testing would be good for a company's public image and provide a vehicle for discussing how they are reducing the use of animals through using alternatives. Development of the roadmap should include stakeholder engagement to identify appropriate metrics. Dr. Casey stated that one goal of the roadmap is to prevent development of methods that will not be used. In response to a question from Dr. Casey, Dr. Berridge indicated that GSK restricts its reports to trends rather than specific animal use to prevent giving detractors opportunities to criticize GSK in the face of a demonstrated progress.

#### ***Additional SACATM Comments***

Dr. Spencer commented that until we have international harmonization, people will continue to conduct animal tests because they will default to the most restrictive test. Reporting annual animal use numbers does not account for this type of factor. While some kind of animal tracking metric, perhaps through estimation, is useful, the goals stated in the roadmap need their own set of metrics for measuring success.

Mr. Janzen asked about the utility of targeting and reducing the use of high-discomfort assays; Dr. Casey responded that these have yet to be well characterized.

Dr. Casey reiterated that ICCVAM is committed to keeping people informed about activities conducted under the roadmap. The three annual opportunities to report on roadmap progress provides incentives for ICCVAM to make progress.

## **IX. Strategic Goal: Use of Timely, Flexible, and Robust Practices to Establish Confidence in the New Methods**

Dr. Jacobs reviewed the three objectives within this goal: (1) clearly delineating testing requirements and context of use, (2) promoting the use of new approaches for establishing confidence, and (3) utilizing public-private partnerships to promote cross-sector communication and cooperation. Regarding context of use, she noted that agencies require specific information to make regulatory decisions; this information may not be derived from any specifically identified test.

### **Establishing Confidence**

#### **Public Comments**

One written public comment was submitted for this section on behalf of PETA.

#### ***Oral Public Comments***

Ms. Sullivan, representing PCRMA, noted that the roadmap does not specifically address methods developed within agencies, and asked that agencies share these methods and the data generated from them with the stakeholder community.



Ms. Groff, representing PETA, noted that a gap exists between the OECD validated methods and their use in the United States. A streamlined approach to establish confidence in new methods would benefit all parties. More data is needed that highlight the predictive value of these methods. She cited the previously mentioned FDA program for medical devices as an example of an effective collaboration with stakeholders. Other FDA collaborations include one with Emulate to explore utility of tissue chip technology. OPP has taken the lead in contributing data to the NICEATM Integrated Chemical Environment (ICE) resource. This data could be used to develop quantitative structure-activity relationship (QSAR) models and establish confidence in in vitro methods. PETA encourages other agencies to share their data within the ICE environment. These types of collaborations have the potential not only to reduce animal use but to advance scientific progress, industry innovation, and improve public health.

***Ad Hoc Comments from Public***

Dr. Birnbaum noted that the National Center for Advancing Translational Sciences (NCATS) has just announced \$15 million worth of grants to develop tissue chips.

***Comments from Designated SACATM Discussants***

There was general agreement among the five SACATM discussants that building confidence in alternative methods will rely on partnerships, including public-private partnerships, and information and resource sharing, including success stories, failures, and challenges. All of this depends on clearly articulated agency needs and requirements.

Dr. Berridge, first discussant, thought that the most effective public-private partnerships are formed around discrete problems, such as specific regulator needs. If human outcomes become the measure of success, we will be challenged by how to achieve validation, qualification, and confidence. Industry has experience with new methods, but they need to find ways to share that knowledge. Dr. Bucher asked Dr. Berridge, if in vitro method development is focused on answering a single, discrete question, are we at risk of overlooking other questions that could potentially be answered by an in vivo study? Dr. Berridge replied that one can use historical attrition data to prioritize testing to the most likely problem areas. Dr. Casey noted that turning the focus away from toxicity testing and toward safety testing may be a practical way to move away from animal testing. Dr. Berridge agreed and added that this would require consideration of exposure limits.

Dr. Coleman, second discussant, cited a 2015 NICEATM workshop on acute toxicity as an example of how to get people together to define a problem and set goals to solve it. This is an example of the public-private partnerships that can address a defined problem. Dr. Casey added that clear articulation of agency needs may provide the sufficient confidence for industry to invest resources to resolve a problem.

Dr. Hamadeh, third discussant, noted that potential new method users need information before they evaluate its technical feasibility, including context of use and agency acceptability. He proposed establishing a forum, possibly agency sponsored, to share information and resources, perhaps incorporating a rating system to communicate a

method's utility. The forum could provide a means for people to share their experiences with a method.

Dr. Milchak, fourth discussant, pointed out that the process for determining the information needed to establish confidence will vary among industries and sectors. Different minimum datasets are required for safety testing than for toxicity testing. International harmonization will be important in determining which alternative methods will be accepted in a global context. Communication between the regulators and the industry could help clarify what constitutes appropriate validation.

Dr. Spencer, fifth discussant, concurred that regulatory acceptance is a central issue, from both a scientific and a policy perspective. We need to identify the policy constraints that will impede acceptance of new methods. Methods that address the needs of several agencies or countries represent the best opportunities for progress. Finally, industry needs to share more of their information; it's not clear exactly how to achieve this, but the concept of the safe harbor could be important here.

### ***Additional SACATM Comments***

Dr. Zhu commented that input from a broad range of stakeholders is important. It would be useful for ICCVAM to publish white paper-like documents to provide progress updates in specific areas and publicize new method developments.

Dr. Williams-Devane suggested a dashboard to show how agencies are using new methods that include information from other countries.

Dr. Willett noted that existing forums for this type of information include the NICEATM and AltTox websites. She agreed that it is important to establish public-private partnerships as well as engage non-traditional stakeholders, including those with an environmental or public health focus. ICCVAM should be as transparent as possible in establishing confidence. This will broaden the spectrum of stakeholders that have confidence in the alternative methods. Dr. Nicole Kleinstreuer directed the audience to Europe's Tracking System for Alternative Methods and Regulatory Acceptance, an online, dashboard driven resource that allows you to see the evolution of various alternative methods. NICEATM is submitting more up-to-date U.S. information to this database.

### **Data Sharing**

Dr. Kleinstreuer, NICEATM Deputy Director, reviewed the roadmap objectives relevant to data sharing including fostering public-private partnerships. She described the recently proposed "FAIR Principles," referring to data that is findable, accessible, interoperable, and reusable, to facilitate collaboration and advancing technologies.<sup>5</sup> These principles were developed with participation from academia, funding agencies, and journal editors. Referring to the previously mentioned Open Data Act, Dr. Kleinstreuer noted that this legislation includes provisions for housing non-public data. The greatest challenges in reaching the FAIR principles are the "interoperability" and "reusability" aspects, which depend on the questions being asked and require

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<sup>5</sup> <https://www.force11.org/fairprinciples>

agreement and cooperation among parties. The NICEATM Integrated Chemical Environment (ICE) resource is striving to adhere to these principles. Some key features of ICE include a structured format, accessibility of data, and flexibility of use. Not all data can be moved and hosted in a centralized repository; finite resources will always determine what data and type of access are prioritized. The June BioMed21 workshop co-organized by NICEATM and HSUS identified some data management practices and goals that would help advance new methods development, including standardized data format, availability and accessibility, and ontological classification. Dr. Kleinstreuer noted that the roadmap themes of communication, collaboration, and commitment are reflected in the major recommendations from the BioMed21 workshop. NIEHS is currently working to create standardized terminologies that will be used across all NIEHS datasets. Data quality is another important element; in compiling rodent uterotrophic data, NICEATM found that only a small proportion of studies could be considered guideline-like. The process for identifying guideline-like studies is very labor-intensive; NICEATM is exploring ways to automate this process. In general, NICEATM is trying to achieve interoperability of data, first among the NIEHS databases and then between them and outside databases.

**Clarifying questions and comments:** Dr. Williams-Devane asked if data sharing discussions are being held with people outside of NIEHS. Dr. Kleinstreuer replied yes, and, as an example, briefly described the NICEATM zebrafish ontologies workshop held in April, which included discussions with a broad range of scientists from academia, industry, and government. In response to a question posed by Dr. Elijah Petersen, NIST, Dr. Kleinstreuer cited the EPA Chemistry Dashboard<sup>6</sup> as an example of a resource that is facilitating the use of data by people using different computational approaches. NICEATM is working with EPA and other resources to support different applications.

## NIH Translator

Dr. Christine Colvis, NCATS, described their Biomedical Data Translator as a tool that reveals connections among existing data; these connections may identify new research and intervention opportunities. NCATS hypothesizes that one of the shortfalls of the current drug development paradigm is incorrect classification of patients based on their signs and symptoms rather than on a biochemical understanding of the disease. The Translator will use a broad range of existing data to answer queries ranging from “Where is this gene expressed?” to “What might be the effect of manipulating this gene?” or “How can clinical trials be designed to study disease subtypes?” The initial goals for the program include defining design and cost, identifying high-value data sources, developing challenging queries, running demonstration projects, and ultimately defining the 10- to 20-year requirements for the Translator. Based on the very ambitious nature of this project, NIH provided NCATS with funding mechanisms that increases their flexibility to support the most productive approaches. Current Translator funding is \$5 million, awarded to five projects encompassing 16 institutions and over 30 investigators. Dr. Colvis reviewed the project timeline to illustrate the dynamic and collaborative nature of the program. The Translator architecture will consist of a

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<sup>6</sup> <https://comptox.epa.gov/dashboard>

blackboard input that draws from various knowledge sources (including sources that potentially include proprietary data), and a reasoning tool that interacts with the blackboard to address a problem iteratively. NCATS recently released a funding opportunity announcement to develop the reasoning tool; creative funding criteria are designed to ensure that successful applicants have the capability to complete the task. A status update will be provided at an October 25 public meeting of project participants.

**Clarifying questions and comments:** In response to a question from Dr. Kleinstreuer Dr. Colvis replied that the response to the reasoner tool Request for Application (RFA) had been good. Dr. Colvis responded to Dr. Casey's question on data sources blinding that NCATS is seeking input on that type of question. Ideally, NCATS would like to iteratively build on previously submitted data for future queries. Dr. Colvis replied to a question posed by Dr. Bolger that NCATS envisions the Translator as a transparent, publicly available tool to make the translation process more efficient; however, it will also have other biological sciences applications. Dr. Petersen asked how reproducibility issues would be handled. Dr. Colvis replied that there are several potential approaches ranging from including only highly curated data to allowing submission of noncurated data on the theory that large amounts of data will automatically indicate the true result. In response to a question from Dr. Mark Miller (NCI) regarding collection of positive and negative data, Dr. Colvis responded that the Translator may be capable of both collecting and weighting positive and negative data. Dr. Miller followed with a second question on the capability of the Translator to handle situations where two labs get different outcomes based on application of different methods. Dr. Colvis indicated that they hope that the Translator will be sufficiently robust to resolve this type of issue. Dr. Casey noted that large datasets that include both positive and negative data could be a valuable resource. Dr. Williams-Devane inquired if the reasoning tool would include a measure of statistical confidence. Dr. Colvis expected that some of the proposals would include a statistical package. Dr. Williams-Devane then asked whether the querying process would be dynamic and able to consider new data. Dr. Colvis replied that they're envisioning a process where each query would draw on all the data available at that time. The NCATS team is considering several issues including reproducibility, data weighting, novel approaches for assigning data attribution and incentivizing data contribution, and the potential publication of finished projects as new knowledge sources.

## Public Comments

There were no written comments submitted on this topic, nor were there any requests for presentation of oral comments.

### **Comments from Designated SACATM Discussants**

Dr. Zhu, first discussant, indicated that while high-quality data sources are very important, especially considering the variability in toxicity data, lower-quality data can also be of value. Examples cited included the NICEATM uterotrophic database, a high-quality resource used to assess estrogenic models and PubChem, a large resource of variable quality data. Including metrics of data confidence would be useful.

Dr. Xu, second discussant, commented that study design, data collection methods, data quality, and statistical methods used for data interpretation are all important considerations that should be included, especially for clinical data.

Dr. Williams-Devane, third discussant, was pleased to see inclusion of metadata as part of the datasets. She expressed concern that intermediate data users (e.g., statisticians, bioinformaticians, and computer scientists) are being overlooked. Additionally, Dr. Williams-Devane encouraged NCATS to collect data that have been identified as acceptable to the agencies. She expressed interest in initiatives that develop new talent in this area so there is a next generation of data scientists.

Dr. Bolger, fourth discussant, expressed appreciation to those agencies that have made their data publicly available. The ICE resource appears to be one mechanism to make data publicly available. When data scientists build a model, they draw on the available data, but there is always room for improvement with more or better data. Therefore, it's important to include a notification system alerting users to updates and improvements to the data resource. Dr. Bolger commented on the importance of data sharing; for example, GSK and Bayer have shared compound structural data and data to support dissociation constant model development, respectively. This kind of data sharing can help with validation of in silico models. Finally, he noted that compiling machine-readable data on individual animals or test subjects is very valuable. Dr. Jacobs noted that Pharmapendium is a source of clinical trial data.

#### ***Additional SACATM Comments***

Mr. Janzen noted that PubChem has been improved by adding controls for quality and reproducibility of assays. For any data resource it is important to be able to distinguish curated from noncurated data.

Dr. Coleman asked whether any ongoing data curation efforts included data from Europe. Dr. Casey indicated that the ICE resource includes data from past validation studies, including some European data. For the endocrine disruptor projects, most of the data were compiled by NICEATM or extracted from the Tox21 or ToxCast projects. The meeting adjourned for the day at 4:30 p.m.

## **September 19, 2017**

Mr. Janzen called the second day of the meeting to order at 9:00 a.m. Participants introduced themselves. Dr. Wolfe read the conflict of interest statement and reviewed meeting logistics.

### **X. Agency Activities**

Dr. Casey introduced the DoD and EPA representatives who would provide updates on their agency activities to reducing animal use in testing. He noted that formal SACATM comment, while not specifically sought, would be useful as feedback to the committee on ICCVAM activities.

## Department of Defense

Dr. Mark Johnson, DoD, provided an overview of the broad range of military research in toxicology. Safety assessment is conducted throughout the DoD compound development process, with the focus of early-stage testing on *in silico* and *in vitro* approaches and limited *in vivo* testing completed only at later stages. The Tri-Services Toxicology Consortium communicates, coordinates, and optimizes toxicology services across DoD. Research includes organ-on-a-chip, AOPs/omics approaches, pharmacokinetic modeling, 3-D cultures and slices, *in vitro* cultures, *in silico*, and *in vivo* studies. Dr. Johnson reviewed the various groups that participate in the consortium and provided examples of their activities, accomplishments, and areas of interest. He also reviewed a broad range of DoD collaborations with other agencies.

## Tox21

Dr. Rusty Thomas, EPA National Center for Computational Toxicology (NCCT), presented the new strategic vision for Tox21. The initial focus of Tox21 was to demonstrate the utility of high throughput screening to address issues facing toxicology: the huge number of untested chemicals, including many environmental chemicals, human relevance, economics, and ethics of animal use. While Tox21 succeeded in demonstrating the utility of high throughput screening, the program now needs to address some of the known deficiencies, including the lack of metabolism, toxicokinetics, validation, and the use of organotypic assays and microphysiological systems. Within their new strategic vision, Tox21 has identified five focus areas: (1) to develop and deploy alternative test systems that are predictive of human toxicity; (2) to address key limitations of current *in vitro* test systems; (3) to curate and characterize legacy *in vivo* studies; (4) to develop a framework for efficient validation of Tox21 approaches; and (5) to refine and deploy *in vitro* methods for characterizing pharmacokinetics. In addition to describing the new focus areas, the strategic vision also provides for a new management approach for Tox21 under which projects will be more focused and collaborative, have specific charters and limited terms, and be reviewed more frequently. Dr. Thomas outlined the new infrastructure teams, noting the addition of a communications team, and briefly described current projects.

**Questions and comments:** Dr. Berridge pointed out that high throughput assays, while successful at addressing toxicity testing throughput and cost issues, have not addressed human predictivity. Organotypic systems can bridge that gap. Dr. Thomas agreed that these systems help provide some organ- and tissue-level context to the effects observed at the molecular level; Dr. Berridge agreed that this is an important part of building confidence in these models.

Mr. Janzen appreciated the Tox21 program's effort to look at true exposure concentrations.

Dr. Willett, referring to the collaborative efforts described in both the DoD and Tox21 presentations, asked what role ICCVAM might play in facilitating such collaborations.

Dr. Casey responded that ICCVAM's role could be to provide a mechanism to bring

groups together and help provide opportunities for collaborations but not to direct activities. Collaboration will happen if it adds value to a project.

## EPA Implementation of Lautenberg Chemical Safety Act

Dr. Gino Scarano outlined EPA's implementation plan for the Lautenberg Chemical Safety Act (LCSA). The LCSA, developed in collaboration with a broad range of stakeholders, was passed by Congress in 2016 with bipartisan support. The act requires EPA to review and determine the risk for new industrial chemicals or significant new uses for existing chemicals. It also gives authority to EPA to review existing chemicals, addressing a major shortcoming of the original Toxic Substances Control Act (TSCA). These activities are to be conducted under clear and enforceable deadlines, without regard to cost or non-scientific consideration, but with consideration of the risks posed to susceptible populations. Review of new chemicals does not require the generation of new data but does require submission of any existing data. These data, and any other available information, in silico predictions, and exposure pathways and information, will be used to determine if a chemical (1) presents a risk, (2) there is insufficient information to make a risk finding, or (3) is not likely to present a risk. In cases where there is insufficient information to make a risk finding, the Office of Pollution Prevention and Toxics (OPPT) may ask the applicant for additional data. For existing chemicals, a prioritization process is conducted. For chemicals found to be of high-priority, a risk evaluation is conducted to characterize their risk as "reasonable" or "unreasonable." EPA will then impose requirements for risk management for chemicals posing an unreasonable risk.

The LCSA explicitly encourages and facilitates the use of methods and approaches that reduce or replace the use of vertebrate animals (including fish) in testing with methods that provide information of equivalent or better scientific quality. Importantly, in many instances, the law replaced the word "data," with "information." The requirement for consideration of the 3Rs applies to information generated voluntarily by applicants as well as information required or requested by OPPT.

LCSA also requires development of a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine or replace vertebrate animal testing for industrial chemicals. The draft goals at this time include (1) reducing and replacing use of vertebrate animals in chemical testing under TSCA; (2) using IATA as a principal approach for evaluating and regulating chemicals under TSCA; (3) collaborating with stakeholders to develop and implement methods that will increase the efficiency of evaluating and regulating chemicals under TSCA; and (4) inspiring industry stakeholders to develop these new methods and strategies. Dr. Scarano reviewed the five draft objectives that will be pursued to meet these goals, including: (1) engage with stakeholders as the Plan is being developed; (2) meet the requirements of the law by collaborating with stakeholders and partners [four separate requirements listed in slides; (3) providing OPPT staff training to understand and use alternative methods and strategies; (4) identify measures of success and (5) communicate with stakeholders and the public throughout the process. Language in the act requires the development of systems that provide "equivalent or better" information than testing in vertebrate animals for ecological species. Finally, Dr. Scarano reviewed

the plan's development timeline, which includes a public meeting in November. Release of the finalized document is planned for June 2018.

**Clarifying questions and comments:** In response to a question posed by Dr. Milchak about developing relationships with industry consortia, Dr. Scarano replied that OPPT is open to both working with existing consortia and fostering new consortia among groups with common interests. EPA could take an active role in fostering collaborations to address known issues or, appropriate industry players may self-organize around identified concerns. Dr. Scarano was unable to address the question regarding specific guidance on TSCA Section 8(e) notification requirements to incorporate alternative methods; it is currently hard to ascertain 8(e) requirements for in vitro or in silico methods.

Dr. Kleinstreuer asked whether the strategic plan or some associated document might enumerate the tests that have been required under TSCA and associate animal numbers with them, to help direct resources appropriately. Dr. Scarano noted that although a worthwhile endeavor, available resources are limited. OPPT has started to compile a list of frequently required or requested tests and plans to capture information related to chemical withdrawals on requests for additional data. Dr. Bucher asked how OPPT will reach internal agreement on what assays are considered adequate for a particular application. Dr. Scarano indicated that those discussions have begun, and training will be key to reaching agreement.

In response to Dr. Mumtaz's question concerning mixtures, Dr. Scarano responded that a variety of ancillary subjects will need to be addressed as the plan is further developed, including mixtures and nanomaterials.

Dr. Lowit observed that animal welfare groups have been good partners for providing training access and funding and they are interested in continuing in that role. Dr. Willett observed a strong similarity between the LCSA and ICCVAM roadmap, and encouraged OPPT to continue communications with ICCVAM and other agencies engaged in similar activities. Dr. Lowit noted that since the passage of LCSA, OPPT has been very proactive about participating in the relevant ICCVAM workgroups.

## XI. Strategic Goal: Connect End-users with the Development of New Tools

Introducing the last of the strategic goals, Dr. Casey noted that agency communication with stakeholders, especially test method developers, will be critical to success of this goal. Past experience with "bottom-up" approaches to test method development is inefficient. Test method developers working with an agency from the start increases their chances for success. The roadmap will only be effective if the agencies are willing to engage the stakeholders, articulate their specific needs, and commit to adopt alternative methods. Rapid change is possible with agency commitment and ICCVAM's role is to facilitate those changes. This will involve identifying anticipated testing requirements, encouraging grant review criteria tailored for the development of alternative methods (for example, R01 grants that encourage alternative methods), and



developing mechanisms to improve communication between end-users and researchers.

## Public Comments

Two written public comments were submitted for this section on behalf of PETA and NA3RsC.

### ***Oral Public Comments***

Ms. Sullivan, representing PCRM, noted the importance of identifying the key areas of need, for example, situations where the animal models fail to provide adequate information. Regulatory agencies and OECD member countries need to identify pathways and endpoints of interest. Framework development is as important as method development. We have considerable data; to use all this data effectively, we need to apply the tools at hand, for example, AOP and IATA frameworks. Agencies, such as OPPT, need to identify what information they need to make decisions and the appropriate tests for producing the required information. Ms. Sullivan encouraged Tox21 to work with OPP and OPPT as they develop the new Tox21 strategic vision and consider how human data, such as epidemiological or clinical trial data, could be incorporated into an AOP-based assessment. She asked for further discussion of the concept of “equivalent or better protections” and to include consideration of the limitations of current animal methods. Finally, the proposed list of available alternative methods is a good communication tool and starting point, but OPPT should also encourage innovation and development of new methods and strategies. OECD is considering a survey to identify the regulatory needs of their member countries. Ms. Sullivan encouraged agency representatives to engage in this OECD process.

### ***Comments from Designated SACATM Discussants***

There was general agreement among the SACATM discussants that improved communications as described in the Roadmap would improve an understanding of the end-user’s requirements. Such communications should be transparent for both the overall process and in guidance documents. The groups of stakeholders targeted by communication efforts should be expanded to include environmental NGOs, patient advocates, healthcare providers, and academic researchers. The discussants also agreed that training, as a communication mechanism, is important, and several topics were proposed including educating stakeholders on the regulatory process and evaluation of computational tools to provide method developers with a sense of end-user’s needs.

The discussants voiced a number of concerns about the grant review process as it is applied to new method development. Dr. Willett suggested that, while the grant review process is complicated, there is room to develop more targeted requests for proposals within the disease-based institutes. NIH, as a large institution, can exert considerable influence. Dr. Xu commented that more transparent articulation of grant review criteria and guidelines as well as training for grant reviewers would enhance their evaluation of assay characteristics and reproducibility. She also recommended increasing the number of reviewers from academic laboratories. Dr. William-Devane added that industry provided data could be useful in developing grants.

Additionally, Dr. Willett, first discussant, reiterated the importance of identifying agency information needs, including legal and regulatory requirements. The proposed OECD survey of regulatory needs for member countries is a great idea. Dr. Casey pointed out that the roadmap implementation plan calls for identification of information needs and regulatory requirements. Dr. Kleinstreuer added that, in the context of specific endpoints, the process will include collection of agency required information as well as information that the agencies will consider for decision making.

Dr. Xu, third discussant, suggested that more review articles discussing recent developments in 3Rs technologies would also facilitate communications.

Dr. Casey further identified a disconnect between bioinformaticians and regulators as a problem that needs to be addressed. A model that has great predictivity but has no regulatory applicability is not going to be used.

### ***Additional SACATM Comments***

Mr. Janzen commented that the goal of grant review criteria is to support the development of new technologies, and these should include mechanisms for commercialization. Dr. Casey responded that those mechanisms exist but are not included in most grants.

Dr. Bucher asked the industry representatives how science could be used to influence the legal adoption of new methods. Mr. Janzen responded that a drug company requires an in vitro panel that is capable of identifying, with confidence, all potential off-target effects. Dr. Spencer added the context of hazard and exposure needs to be considered to address regulatory requirements. Assessing exposure is an important approach to fill information gap without using assays. IATAs could be useful in material safety evaluations. Dr. Milchak hoped that lawyers would support a new method if scientists judge it sufficiently informative. On the other hand, there may be legal risk to the regulators in accepting a new method. Dr. Jacobs noted that, for legal responsibility, it's important to consider the consequences of being wrong.

Dr. Milchak noted that manufacturing companies are end-users of new assays; if a new method works, a company will use it. However, many methods are not generalizable and are fit for purpose based on specific chemistries or product types. End-users would benefit from a forum where context of use details can be discussed with method developers. Dr. Petersen noted that situations exist where modifications are acceptable to test difficult chemicals; perhaps this approach could be applied more broadly.

Dr. Casey noted that one of the best way to establish confidence in a new method is to demonstrate its success in a non-regulated space; the question then becomes how to encourage use in that space.

Dr. Becker commented that sharing success stories can facilitate establishing confidence; we need a structure to communicate these stories.

Dr. Mumtaz noted that, in regulatory contexts, often the goal is to determine safe

exposure levels. Convincing people that new alternative methods can perform as well as or better than animal models may be accomplished, in part, by demonstrating how in vitro or high throughput data can be used to determine those safe exposure levels.

### Presentation: NIEHS Grant Opportunities

Dr. Daniel Shaughnessy, NIEHS, reviewed the general scope of the NIEHS small business grant opportunities for alternative methods development, noting that Small Business Innovation Research (SBIR) and Small Business Technology Transfer grants (STTR) are available only to U.S. businesses with fewer than 500 employees. SBIR/STTR opportunities typically begin with feasibility studies (Phase I) studies that form the basis for the full research and development grants (Phase II). Some agencies also support commercialization (Phase III) efforts; however, NIH does not usually participate in Phase III awards. It is expected that companies will commercialize their technologies with non-SBIR resources. Opportunities exist for investigator-initiated (unsolicited) applications through the Department of Health and Human Services omnibus announcement. Dr. Shaughnessy reviewed one of the specific NIEHS SBIR/STTR areas of interest: alternative methods for toxicity screening, testing, and modeling, with emphasis on methods that encompass genetic diversity and reduce animal use. He described some projects that have been funded under the SBIR/STTR omnibus announcement. The other funding avenue is through specific Requests for Applications (RFAs), which are solicitations issued with a specific goal and for which a special emphasis panel is convened to review the applications. Dr. Shaughnessy closed by highlighting three current NIEHS RFAs relevant to alternative methods development, namely development of assays for evaluating the effects of toxicants on cell differentiation, validation of alternative methods for toxicology testing, and developing organotypic models derived from experimental animals used in toxicology testing.

### *Ad Hoc SACATM Comments*

Dr. Willett felt that these small business grants could be directed towards solving known problems, such as incorporating metabolism into in vitro assays, rather than supporting a technology. She was concerned that the further investment in animal organ technologies implies a degree of confidence in legacy animal data that may be unwarranted. Dr. Willett added that it is important that awardees for these grants expand our understanding on a molecular level. High-quality data should be collected and made publicly available. Materials for these studies need to be obtained as humanely as possible, and consideration given to the use of organ chips platforms for these types of applications, with an eye towards using these systems in the future to replace animal testing entirely. Dr. Willett suggested that NIEHS explore the use of alternative funding mechanisms like those described by NCATS for Phase II awards. Finally, she encouraged ICCVAM to conduct retrospective analyses of toxicity models to assess the value of legacy models. Humane Society International has supported analyses focused on disease models, and published review articles summarizing the findings and appropriate suggestions for the use of alternatives in the future. In short, with the limited resources available, and it is important to focus on approaches likely to yield the most benefit to public health and the environment. Dr. Shaughnessy responded that one of the projects he described involves an in vitro to in vivo

comparison, with the goal of reducing animal use. These could, for example, replace animal use in early drug development. Data sharing is more difficult; small businesses are reluctant to share data early in the development process. For the SBIR/STTR grants, awardees are encouraged to begin working with the agencies early to ensure their assays meet a regulatory need. Getting agencies involved at the Phase IIb stage is a little late in the process but the agency input is still helpful. Businesses are open to input from the entities that will eventually use their assays; letters of support from these entities can provide an advantage to a grant application. The more conversations the small business have with the end-user, the better.

Dr. Thomas noted that the EPA NCCT is running a challenge to retrofit high throughput screening assays with metabolic competence; results will be announced soon. Some assays under development might benefit from the addition of a metabolic competence feature; such an addition would also improve their relevance. Approaches to facilitate these collaborations were discussed.

Dr. Casey noted that discussions of whether we should be developing preclinical species-on-a-chip or humans-on-a-chip reiterates the point that we're trying to do two different things at the same time: move away from animal testing and improve human predictivity. The primary directive embodied in the roadmap is to understand what the customer wants, and the customer (that is, pharma), is asking for is microphysiological systems for preclinical evaluations. Dr. Berridge added that such a step should be considered as a part of the process away from animal testing; there's immediate value of having an animal-based tissue chip because most compounds fail in the preclinical stages. These systems would also support development of IVIVE models. Mr. Janzen agreed that the human-on-a-chip stage is going to be reached, but the animal on a chip should come first.<sup>7</sup>

## XII. Implementation of the Strategic Roadmap

Dr. Kleinstreuer introduced the final session on implementation of the roadmap. The general framework for implementation includes six key endeavors: (1) coordinating and prioritizing activities around ICCVAM workgroups, (2) drafting a scoping document to identify U.S. agency needs, (3) coordinating efforts with stakeholders, in which public-private partnerships are going to be key, (4) obtaining and curating high-quality data from reference methods, (5) identifying and evaluating non-animal alternative approaches, and (6) gaining acceptance and facilitating the use of non-animal approaches. She noted that ICCVAM has strong commitment from federal agency partners for these activities, citing the DoD-commissioned National Research Council report and EPA's goal to eliminate animal testing for the six-pack as examples.

### Alternatives for Skin Sensitization Testing

Dr. Joanna Matheson, Consumer Product Safety Commission (CPSC), introduced the ICCVAM Skin Sensitization Workgroup (SSWG). This workgroup consists of over 20

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<sup>7</sup> Mr. Janzen's comment was not audible on the videocast recording and so could not be reviewed and confirmed after the meeting.

members from six federal agencies plus ICATM liaison members. She noted the contributions DoD has made toward advancing alternative method implementation. To meet their initial charge, the SSWG developed three computational models that predict skin sensitization hazard and potency based on non-animal and chemical structure inputs. Current SSWG efforts are directed towards drafting a scoping document summarizing agency requirements for skin sensitization data for publication. This document highlights the variability among agency information needs.

As an example of how ICCVAM engages stakeholders, Dr. Matheson summarized SSWG participation in a 2016 ICATM-sponsored workshop to assess regulatory requirements and available alternatives approaches for skin sensitization testing. Workshop products included a white paper characterizing regulatory requirements for skin sensitization testing, a position paper summarizing workshop outcomes and ICATM recommendations, a proposal to OECD for development of a performance-based test guideline for defined approaches to testing and assessment of skin sensitization, and plans for future ICATM workshops. The 2016 workshop identified a key need for information about the commercial availability and vendor capabilities for conducting specific methods, reiterating points made previously about making information more available.

While ICCVAM already has a robust skin sensitization database, ongoing efforts include collection of paired in vitro and murine local lymph node assay (LLNA) data, additional LLNA data to assess assay variability, and additional human data to help evaluate defined approaches. Expanding on this last point, Dr. Matheson pointed out that the predictivity of animal tests relative to human hazard and potency are approximately 70% and 60%, respectively. The poor performance is due in large part to animal data variability. NICEATM collaborated with Cosmetics Europe to assess the performance of 12 non-animal testing strategies based on the OECD AOP for skin sensitivity initiated by covalent binding to proteins and found most of them to be superior to the LLNA in predicting human hazard and potency.

Dr. Petersen described a CPSC-NIST validation study to assess the performance of the Electrophilic Allergen Screening Assay, including how it performs with challenging test substances. Preliminary technical findings focused on aspects such as managing light-sensitivity of reagents, positive control chemical concentrations, and physical laboratory setup to optimize reproducibility. Future efforts will include developing calibration standards, identifying intermediate process measurements to improve troubleshooting, and translating to a 96-well plate format.

Dr. Matheson discussed some approaches for gaining regulatory acceptance. In addition to submitting a proposal for a performance-based test guideline for defined approaches to skin sensitization testing to the OECD, the SSWG is exploring expansion of chemical space coverage for a defined approach by using in vitro methods. Under this project, NTP will be testing approximately 200 chemicals nominated by ICCVAM agencies.

In closing, Dr. Matheson reviewed the challenges inherent in these activities: animal data of varying quality used as reference data; the inconsistent data requirements across U.S. and international agencies; limitations in chemical space coverage; limited commercial availability of alternative tests; and regulatory and institutional inertia. Education, training, and collaboration with internal and external partners will be key to overcoming these challenges.

**Clarifying questions and comments:** Dr. Berridge asked about the source and nature of human data provided to CPSC. Dr. Matheson replied that CPSC doesn't require data submissions but the repeat insult patch test is a frequently used protocol. In response to a question posed by Dr. Coleman, Dr. Matheson replied that QSAR modeling is used in published defined approaches. When Dr. Willett asked for details about the more challenging materials included in these studies, Dr. Kleinstreuer replied that natural products and pesticide formulation products were included in the Cosmetics Europe and NTP studies, respectively. While nanomaterials have not yet been considered, ICCVAM is trying to provide a broad range of chemical types and use cases. Dr. Matheson responded to a question posed by Dr. Bolger that the KeratinoSens system models the dermis layer. While not assessed in the defined approaches described here, other available methods assess skin penetration and the skin irritation necessary to induce skin sensitization. Dr. Kleinstreuer added that Cosmetics Europe has put a lot of effort into evaluating dermal penetration and absorption assays. Following on a different point, she noted that an assessment of the Cosmetics Europe data showed that the predictivity of animal data to the human response is almost exactly the same as the reproducibility of the animal test itself. This suggests that you might use reproducibility of the animal data as a surrogate for predictivity of the human data.

## Public Comments

One written public comment was submitted for this section on behalf of PETA.

### **Oral Public Comments**

Dr. Esther Haugabrooks, representing PCRM, expressed their support for the development of specific method and endpoint implementation plans, which will help encourage adoption and use of NAMs by federal agencies. She encouraged collaboration with international partners to facilitate global harmonization and efforts to harmonize guidance and requirements across the U.S. federal agencies. In addition to communication, resources should also be made available for industry incentives, regulatory training, and method development. Proposed scoping exercises should include a discussion of partial replacement efforts directed towards specific classes of chemicals, and include examples of success stories. Speed is often more important than cost for some regulated industries, so prioritization of submissions using alternative methods could be an effective incentive. PCRM encouraged ICCVAM to include strategies for incentivizing use of alternatives in the scoping documents. Training on alternative method use needs to be made available for both regulators and submitters. While refinement is one of the 3Rs, PCRM does not support the inclusion of refinement objectives in the implementation plan; reduction approaches should be prioritized and replacement identified as the ultimate goal. In closing, she noted that stakeholders look forward to the adoption of the defined approaches for skin sensitization testing by U.S.

agencies as full replacements for animal tests independent of OECD action.

***Comments from Designated SACATM Discussants***

Dr. Bolger, first discussant, appreciated the information about specific work efforts. He asked how a regulator would interact with a software company to include their QSAR skin penetration models in validation studies. Dr. Casey responded that companies with a product or resource that could add value to an ICCVAM approach of interest should contact us. Dr. Kleinstreuer added that there are commercial software platforms being used as part of these defined approaches. The best way to increase awareness of available tools is to publish them and bring them to the attention of the appropriate ICCVAM working group. Dr. Matheson noted that the ICATM partners often alert ICCVAM to the availability of new methods. This highlights the need for a central resource for information about new methods. Dr. Bolger further commented that data from mechanistic in vitro assays evaluated against chemical representatives of a large chemical space might support mechanistic modeling of skin sensitization. Dr. Matheson responded that the next step in this effort is to assess skin sensitizers that work through different mechanisms.

Dr. Milchak, second discussant, while praising the progress made on this endpoint, noted the physicochemical incompatibility of many chemicals of interest with available test methods. 3D human tissue models currently under development would be a good platform on which to test these products. Dr. Jacobs agreed and noted that many cosmetic formulations have difficult chemical properties.

Dr. Williams-Devane, third discussant, was concerned about the criteria used to determine data quality and if there is consensus regarding these criteria. These criteria should be made publicly available. Similarly, when assembling a list of acceptable test methods, inclusion criteria should be transparent and publicly available. Dr. Kleinstreuer responded that the intention is to make all processes as transparent as possible. For data, we use very well-defined criteria, including test guidelines, and get input on criteria from ICCVAM workgroups and subject matter experts. Decision criteria are made public along with the data. We are currently developing criteria for developmental toxicity assessments. The goal is to consider all applicable methods, and input from public meetings like this is important. Anyone aware of a method that might be useful should bring it to the attention of either ICCVAM or their relevant regulatory agency. Dr. Williams-Devane asked if methods from the literature were being considered or just nominations; Dr. Kleinstreuer replied that both are considered.

Dr. Coleman, fourth discussant, noted that, for medical devices, aqueous and oily solvent extracts are used to simulate what happens when a device is inserted into a human body. In vitro methods work better with aqueous extracts than with oily ones; in the absence of 3D models formally validated for medical devices, industry is interested in approaches that could be used to address this problem. Industry prefers access to open-source methods.

### **Additional SACATM Comments**

Dr. Spencer praised the collaborative nature of this effort. Anything that can be done to ensure that chemicals are correctly classified under GHS is helpful. Dr. Hamadeh, however, noted that it is unclear how ICCVAM is engaging the end-user in the implementation plan.

### **Alternative to Acute Systemic Toxicity Testing and Other Areas**

Dr. Kleinstreuer introduced the ICCVAM Acute Toxicity Workgroup as the entity responsible for the acute oral toxicity testing implementation plan. This Workgroup includes over 20 members from eight agencies, including a large participation by DoD, for which this endpoint is very important. While the rodent LD50 endpoint remains important to the regulatory community, Dr. Kleinstreuer reviewed the various U.S. agencies uses of acute oral toxicity data, illustrating the different decision contexts that exist among and, in some cases, within agencies. Workshops largely represent ICCVAM's efforts at stakeholder coordination. One example is the 2015 NICEATM-organized workshop on acute toxicity testing.<sup>8</sup> A second workshop focused on acute toxicity was held at World Congress in August 2017. Areas of discussion included regional updates, the U.S. roadmap development, industry perspectives, and international harmonization. Efforts are currently underway by NICEATM and EPA NCCT to assemble and curate a large dataset of LD50 values, which has provided insights on data variability. Like the skin sensitization data, there is variability across multiple hazard classifications. Dr. Kleinstreuer further described NICEATM efforts to extract data on over 800 EPA pesticide formulations; these data will be made available in ICE next month. Past studies indicated that no single in vitro test can predict acute toxicity; however, they can be used to set starting doses. Analysis of high throughput screening data showed that combinations of these assays fail to adequately predict in vivo lethality. High throughput screening assays often fail to include effective in vivo doses or assays specific to the targeted toxicity. However, structure-based models are better at predicting in vivo outcomes, suggesting that combining high throughput and structure-based approaches could be more effective than either one alone. NICEATM is asking for submissions of QSAR models for predicting acute oral toxicity, and we have asked ICCVAM agencies to specify appropriate criteria. Results of this effort are planned for presentation in April 2018. Among other approaches for reducing animal use, the EPA waiver on acute dermal toxicity is expected to save over 2000 animals per year and is being adopted internationally. Challenges to reducing and replacing animal use for acute systemic toxicity include variability of the reference data, variability and ambiguity of data requirements, and overcoming institutional inertia.

Dr. Kleinstreuer concluded her presentation by noting that ICCVAM has established three new workgroups focused on in vitro to in vivo extrapolation, developmental and reproductive toxicology, and read-across. The scope and charge of these workgroups is still being finalized.

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<sup>8</sup> Workshop report: Hamm et al., *Toxicol In Vitro* 41:245-259, available at <https://www.ncbi.nlm.nih.gov/pubmed/28069485>.



**Clarifying questions and comments:** In response to a question posed by Dr. Willett, Dr. Kleinstreuer indicated that having expert input on modes of action is very important to the QSAR models. NICEATM plans to develop local models for specific toxicity mechanisms, chemical classes, and use cases.

Dr. Zhu asked for details on the data release for the QSAR model solicitation. Dr. Kleinstreuer responded that a training set (80%) will be initially released for model development and the remaining data (20%) will be held back for method evaluation. Former EPA staff who have experience with this type of solicitation are collaborating with NICEATM in this effort.

Dr. Petersen asked Dr. Kleinstreuer to speculate on the source(s) of the variability in the animal data; she responded that a clear source has not yet emerged. This variability, however, will affect how summary metrics for training models should be chosen. NICEATM is still seeking input on this but are considering first excluding outliers and then choosing the lowest remaining LD50 value. Dr. Petersen noted that the variability of the data might affect the size of the bins, and Dr. Kleinstreuer agreed that agencies should take that into consideration. In response to a question posed by Dr. Jacobs, Dr. Kleinstreuer indicated that characteristics such as age, weight, strain, and vehicle have been considered as sources of variability when possible, but that information is not always available. Dr. Coleman asked if gastric absorption is considered in these evaluations. Dr. Kleinstreuer responded that NICEATM considers that information when available.

Dr. Miller asked how changes in gene expression observed in cultured cells will be accounted for. Dr. Kleinstreuer commented that it is hard to compare in vitro and in vivo systems; however, NICEATM has been conducting IVIVE analyses to assess relevant exposure levels.

In response to a question posed by Mr. Janzen, Dr. Kleinstreuer indicated that Tox21 does not include a permeability assay.

Dr. Milchak asked if computational approaches represented results of one QSAR approach or a combination of approaches. Dr. Kleinstreuer responded that the EPA TEST tool was used to provide a consensus of QSAR approaches for about 3000 chemicals. NICEATM's intention with the model solicitation effort is to identify the best-performing models and summarize the model estimates for both point estimates and classification group. Dr. Casey added that the 80-90% figure represents a spread around a point estimate rather than concordance with classification.

Dr. Jacobs noted that not all LD50 study deaths have the same cause. Dr. Kleinstreuer agreed and expressed a hope that mechanistically based local models will help address that.

## Public Comments

Three written public comments were submitted for this section on behalf of the University of Pittsburgh, PETA, and NA3RC.

### ***Oral Public Comments***

Dr. Amy Clippinger, representing PETA, noted that a 2016 workshop co-organized by PETA and NICEATM on inhalation toxicity resulted in four major recommendations. Working groups were established around each of the recommendations. The activities of these groups are still ongoing, and Dr. Clippinger invited participation on these groups by interested agencies. Major activities include clarifying agencies' needs and evaluating how new approaches could improve on animal tests in protecting human health. She encouraged agencies to share inhalation data with NICEATM. Finally, Dr. Clippinger reiterated the importance for training for academics as well as regulators, and announced an SOT In Vitro and Alternative Methods Specialty Section webinar on validation planned for October.

### ***Comments from Designated SACATM Discussants***

Dr. Coleman, first discussant, shared that the test used for medical devices is a mouse tail vein injection of a medical extract to assess behavioral and pathological endpoints. It is very rare to observe lethality; the failure rate is less than 1%. She proposed repurposing some of ICCVAM's approaches as possible replacements for this test. Dr. Milchak, second discussant, noted that most of 3M's LD50 studies are done for regulatory purposes. The resulting information is not very useful for safety or risk assessment because most chemicals tested are relatively nontoxic. More helpful approaches include, for example, waivers for compounds or specific chemistries that fail to be absorbed in sufficient levels to cause toxicity. In vitro cytotoxicity assays are of limited utility as many of our chemicals are insoluble and fail to work well in two-dimensional cell culture. 3M, for example, would like to find an alternative approach, either from a delivery or modeling perspective, that improves assay utility. In general, the LD50 is an archaic assay that has little bearing on safety; it is good to see efforts to replace it.

Dr. Zhu, third discussant, commented that different strategies will be needed to develop models for point estimates and categorical classification. He suggested that a categorical classification model might be less sensitive to data quality. Simply identifying toxic compounds might be a more attainable goal. Finally, he recognized that current efforts are focused on predicting rat toxicity, but eventually we will want to use these approaches to predict human toxicity; he encouraged consideration of how these models might be used in that context.

### ***Additional SACATM Comments***

Dr. Hamadeh hoped that the same diligence exhibited here is applied to efforts in developmental toxicology. Dr. Jacobs concurred with the opinion that the LD50 is of limited utility in many cases and consideration should be given to whether it is actually needed. Dr. Kleinstreuer responded that the current work was done in response to agency requests. Dr. Lowit added that the goal is to replace the lethality endpoint with something more science-based. There was general discussion about the limitations of the LD50 as a test for toxicity. Dr. Willett noted that one approach is to use science-based evaluations as a basis for arguing that laws should no longer require the LD50 test but use something that's based more on mode-of-action and is more flexible for making decisions. We're moving into a paradigm of predicting safety and not toxicity; it

is important to revisit the regulations.

### **XIII. Adjournment**

Mr. Janzen thanked everyone for their participation. Dr. Bucher thanked participants for their well-considered comments and felt that the roadmap would benefit from the feedback shared at this meeting. He asked attendees to promote the roadmap. Dr. Casey also thanked attendees for their time, participation, and input. The discussion about the LD50 highlighted that these issues go beyond science, which makes them particularly difficult to address. Drs. Lowit and Jacobs also expressed their appreciation for the useful feedback, and thanked Dr. Casey for his leadership. Finally, Mr. Janzen noted and expressed his appreciation for the spirit of cooperation between the agencies and NGOs. The meeting was adjourned at 3:40 p.m.

*Summary Minutes from the September 18-19, 2017, SACATM Meeting  
NIH, Bethesda, Maryland*

These summary minutes have been read and approved by the Chair of the Scientific Advisory Committee on Alternative Toxicological Methods as certified below.

Date: November 28, 2017



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Mr. William P. Janzen

Chair of SACATM