

Update on ICCVAM Activities

Background Materials:

- ICCVAM Vision Document
- 15 Years Out: Reinventing ICCVAM. Birnbaum L. *Env Health Perspect* 121(2) 2013
- ICCVAM 2012- 2013 Biennial Report
- The AOP for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 1: Scientific Evidence. OECD (2012)
- The AOP for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 2: Use of the AOP to Develop Chemical Categories and Integrated Assessment and Testing Approaches. OECD (2012)
- FR Notice: Request for Information on Alternative Skin Sensitization Test Methods and Testing Strategies and for Comment on ICCVAM's Proposed Activities
- Responses to FR Notice
- Development of Integrated Testing Strategies to Identify Potential Sensitizers

Introduction: Update to the 2013 Draft ICCVAM Vision and Direction

In September 2013, ICCVAM developed and published on its website the draft document *A New Vision and Direction for ICCVAM*, which communicated a change in how the committee would operate and the activities it would undertake. The new vision and direction responded to a change in philosophy for ICCVAM and NICEATM that was announced in January 2013 by Dr. NIEHS and NTP Director Dr. Linda Birnbaum. Briefly, the draft document presented (1) areas for immediate priority and scientific focus, (2) plans for improved communications with stakeholders, and (3) a proposed role in exploring new paradigms for the validation and use of alternative toxicological methods.

Since the 2013 SACATM meeting, both NICEATM and ICCVAM have been working diligently to implement the draft vision and direction document. The draft has not been updated or revised *per se*. Instead, NICEATM and ICCVAM are considering options for a mechanism to regularly update the public on priorities and projects; stakeholders have suggested using a web-based approach that can be readily updated. At the September 2014 SACATM meeting, NICEATM and ICCVAM look forward to input from their advisors and the public on ICCVAM's progress towards implementing the draft vision and direction document and on additional scientific areas for NICEATM and ICCVAM to consider pursuing. In addition, individual agencies will provide updates to SACATM on agency-specific activities related to implementing the 3Rs (i.e., replacement, reduction, and refinement of animal use).

1. **Areas of priority and scientific focus for immediate resource investment:**

In 2013, ICCVAM set as priorities three areas: acute toxicity, vaccine potency and safety, and skin sensitization testing, based on their likelihood for successful implementation into regulatory use.

ICCVAM's progress for each is provided below.

Acute Oral and Dermal Toxicity Testing

NICEATM and the Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) are collaborating to evaluate the relative contribution of data from acute oral and dermal toxicity tests to pesticide hazard classification and labelling. A draft dataset of acute oral and dermal LD₅₀ data for formulations of a variety of pesticides, including conventional pesticides, antimicrobials, and biopesticides, is nearing completion. The formulations being tested span all four EPA hazard categories for acute toxicity (I, II, III, IV). Once the database is fully curated and quality control processes are completed, NICEATM will conduct statistical analyses that should allow the EPA to determine the relative contribution of data generated from oral and dermal LD₅₀ tests to final pesticide labeling. Availability of the draft statistical analysis and dataset for public comment will be announced via the *Federal Register* in Fall 2014. In addition, NICEATM and EPA/OPP are discussing additional projects related to reducing use of laboratory animal testing for pesticide testing, particularly for the assessment of acute toxicity.

Vaccine Potency and Safety Testing

The Animal and Plant Health Inspection Service (APHIS) of the US Department of Agriculture (USDA) is developing ways to use fewer hamsters in the maintenance of *Leptospira* challenge cultures. The effects of this change in hamster usage is being monitored over the next 5 years by collecting, tracking, and interpreting information regarding hamster usage from annual reports. Up-to-date metrics will be provided as they become available.

NICEATM and ICCVAM are working with the International Working Group for Alternatives to HIST [the murine histamine sensitization test] to organize a workshop on August 24, 2014, that will bring together scientists to review and discuss the implementation of *in vitro* assays as alternatives to the HIST for the testing of acellular pertussis vaccines. The workshop will also provide a forum for reviewing the current framework for regulatory acceptance of a harmonized approach for alternative *in vitro* assays to HIST, in the context of recent international progress in the development of such alternative assays.

Skin Sensitization Testing

Fostering the evaluation and promotion of alternative test methods for regulatory use in skin sensitization hazard assessment has been one of ICCVAM's long-standing priorities. Because the adverse outcome pathway (AOP) for skin sensitization is well characterized, and a number of non-animal test methods have been developed, it has promise for the near-term development of testing strategies that do not require the use of animals. Later this year, the Organisation for Economic Co-operation and Development (OECD) should finalize new test guidelines in the area of skin sensitization based on two non-animal methods, the direct peptide reactivity assay (DPRA), and the KeratinoSens™ assay. In a November 2013 [Federal Register \(FR\) notice](#), ICCVAM requested information about test methods, testing strategies, and other information relevant to identification of potential skin sensitizers. [Comments](#) in response to this notice provided information on several *in vitro* assays under development, and encouraged ICCVAM to foster collaborations and focus

efforts on methods most likely to achieve future regulatory acceptance. ICCVAM reconstituted and re-invigorated the skin sensitization working group (SSWG) to: (1) provide expertise in the design and examination of the predictive value of a battery of *in vitro* and *in silico* methods and (2) contribute to the evaluation of methods and approaches for skin sensitization testing nominated to ICCVAM in the future, or submitted to international partners as part of the International Cooperation on Alternative Test Methods (ICATM) process.

Highlighted among the many efforts in this area is the ongoing curation of a database for over 100 substances evaluated with DPRA, human cell line activation test (h-CLAT), KeratinoSens™, and murine local lymph node assay (LLNA) that have been characterized by physicochemical characteristics and range of LLNA potency. Once completed, the database will be divided into a training set to build computational models, and a test set to subsequently evaluate the models and determine the optimal decision strategy.

Other ICCVAM or NICEATM activities in this area include the following:

- ICCVAM' consideration of a nomination from the National Institute of Occupational Safety and Health to assess the electrophilic allergen screening assay, a test method that identifies electrophilic substances that may produce skin sensitization by measuring their tendency to bind to skin proteins, the first key event in the AOP.
- NICEATM collaboration with academic scientists to develop and evaluate chemical structure–activity relationship (SAR) models to predict skin sensitization.
- NICEATM collaboration with industry scientists to develop an open-source Bayesian network as an operational framework for an integrated testing strategy that uses multiple physicochemical, *in silico*, *in chemico*, and *in vitro* inputs to predict skin sensitization properties of test substances (<http://ntp.niehs.nih.gov/go/its>).
- NICEATM evaluation of various high-throughput screening assays for skin sensitization in coordination with NIEHS Tox21 activities.

Charge Questions for SACATM:

- Please comment on ICCVAM's progress, to date, in carrying out the priority areas of work described in the ICCVAM vision and strategy document.
- Please comment on whether there might be additional short to intermediate term (1-5 years) scientific areas that ICCVAM and NICEATM should consider pursuing.