Update on ICCVAM Activities

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SACATM Meeting, September 2, 2015
Research Triangle Park, NC

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

Background

- The 2013 document, "*A New Vision and Direction for ICCVAM*," describes the *initial steps* towards a new strategic direction for ICCVAM and NICEATM.
  - Member agencies taking a more active role in priority setting and operations of the Committee.
  - Change in approach:
    - Streamline the number of active projects where the science has advanced
      - There is a reasonable likelihood of success with a reasonable timeframe (1-5 years) for implementing into regulatory use.
    - Maintain flexibility to reorient efforts to maximize potential progress towards use of alternative approach

Background

- Priority areas for work:
  - Initially three projects were been identified
    - Biologics: Leptospira vaccine potency
    - Acute oral and dermal toxicity testing
    - Skin sensitization
  - Recent expansion of projects
  - Improve communications with stakeholders and the public &
  - Improve international harmonization
  - Explore new paradigms for the validation and utilization of alternative toxicological methods

Update on FY 2015 Priority Areas

- Test method evaluation activities
  - Acute toxicity testing
  - Biologics testing
  - Skin sensitization testing
  - Endocrine disruptors testing
- Communication
  - Communities of practice
  - Public forum
  - Other stakeholder interactions

Update on FY 2015 Priority Areas

- Implementing alternatives for vaccines
  - Carol Clarke and Richard McFarland (10:45)
- New Paradigms for Validation: Performance Based Validation
  - EDSP; David Dix (10:45)
- International Collaborations
  - Abby Jacobs (12:30)
- New Initiatives
  - Tracking metrics (Anna Lowit - 1:30)
  - 3Rs Roadmap (Warren Casey - 2:45)

Priority Area: Acute Toxicity Testing

- Finalize statistical analysis of the relative contribution of data from acute oral and dermal toxicity tests to pesticide hazard classification and labelling
  - Completed in FY2015.
  - FY2016 EPA will release of statistical analysis & implication for waivers
- Assist federal agency efforts to implement alternative assays related to eye irritation, skin irritation, and skin corrosion
  - EPA updated guidance on a non-animal testing scheme for assessing eye irritation potential of EPA-registered antimicrobial cleaning products.
  - Provides a non-animal approach to identify Category I-III eye irritants

Priority Area: Acute Toxicity Testing

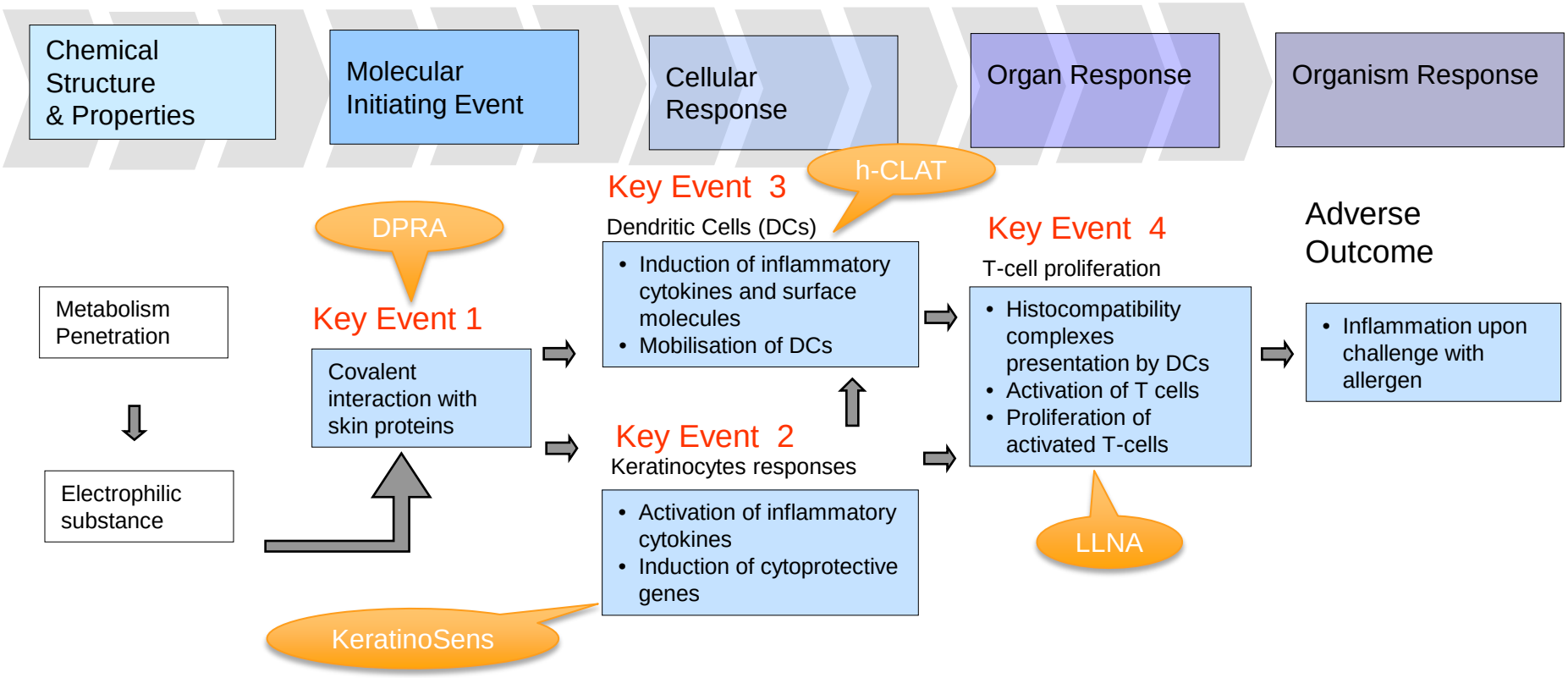
- Initiate projects related to reducing use of laboratory animal testing for the assessment of acute inhalation toxicity
  - Workshop on *In vitro* methods to assess the inhalation toxicity of nanomaterials with PETA held February 24-25, 2015, Washington, DC (Elizabeth Maull to discuss later today)
- Multiple agencies moving to reducing animal use in acute testing, lethality testing & eye irritation, skin irritation, and skin corrosion
  - NICEATM supporting EPA to develop a Road Map for replacing *in vivo* testing with alternative approaches
  - Workshop on Alternatives to Acute Oral Toxicity Testing to be held September 24-25, 2015, NIH Bethesda, MD

NRC Report for DoD

Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense

- Conceptual approach for DOD to develop a predictive toxicology system
- Reviews the current state of computational and high-throughput approaches for predicting acute toxicity
- Suggests methods for integrating data and predictions
- Lessons learned from current high-throughput screening programs
- Suggestions for DOD investment

OECD Adverse Outcome Pathway (AOP) for Skin Sensitization[1]



[1] For sensitization that is initiated by covalent binding to proteins.

OECD 2012. Guidance Document No. 168: The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins: Part 1, Part 2.
http://www.oecd.org/chemicalsafety/testing/seriesontestingandassessmentpublicationsbynumber.htm

Priority Area: Skin Sensitization

- Produce and test an integrated decision strategy for skin sensitization using
  - Physicochemical properties
  - An *in silico* method (OECD QSAR Toolbox)
  - The three *in chemico* or *in vitro* assays validated by EURL ECVAM
    - DPRA, KeratinoSens, and h-CLAT
- Machine learning: Artificial Neural Network (ANN), Bayesian Network (BN), Classification and Regression Tree (CART), Linear Discriminant Analysis (LDA), Logistic Regression (LR), Support Vector Machines (SVM)
- Predict skin sensitization (yes/no) based on LLNA and human results

Example Model: LLNA Skin Sensitizers

SVM with h-CLAT + OECD + 6 PhysChem Properties

		LLNA NEG	LLNA POS
Model	NEG	25	2
	POS	1	66

Training set

		LLNA NEG	LLNA POS
Model	NEG	7	1
	POS	0	18

Test set

	Training set	Test set
Specificity %:	96.2	100
Sensitivity %:	97.1	94.7
Accuracy %:	96.8	96.2

- Conclusion: machine learning models are superior to individual assay methods or battery, and achieve better balance between sensitivity and specificity.

Example Model: Human Skin Sensitizers

SVM with all assays + Log P

MODEL \ HUMAN	NEG	POS
NEG	21	1
POS	0	50

Training set

MODEL \ HUMAN	NEG	POS
NEG	9	1
POS	0	14

Test set

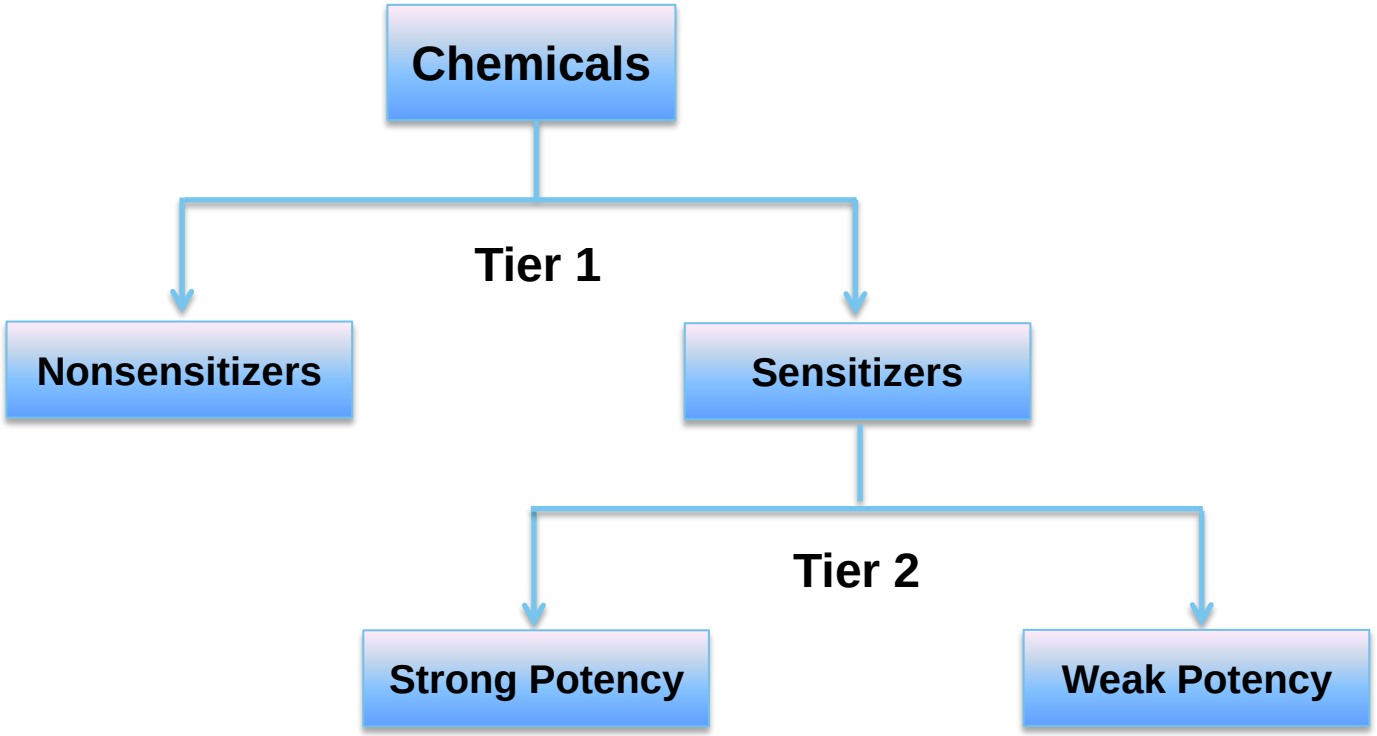
LLNA \ HUMAN	NEG	POS
NEG	6	0
POS	3	15

LLNA vs Human for test set

	Training set	Test set	LLNA vs Human for test set
Sensitivity %:	98.0	93.3	100
Specificity %:	100	100	66.7
Accuracy %:	98.6	95.8	87.5

- Conclusion: machine learning models are superior to individual assay methods or battery, and achieve better balance between sensitivity and specificity.

Next Step: Modeling Strategies for Potency



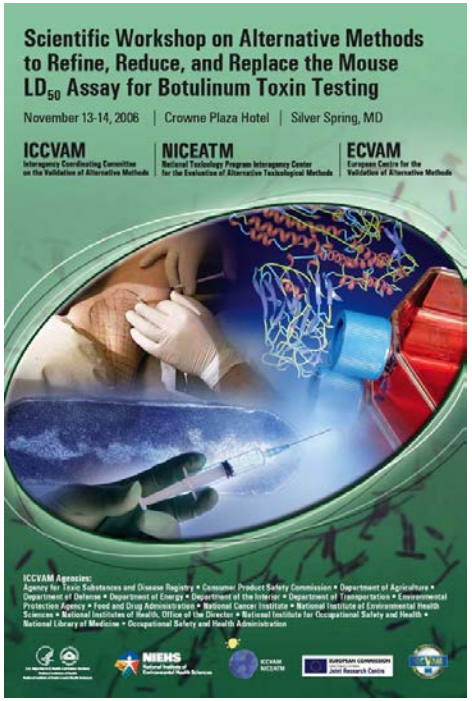
Priority Area: Endocrine Disruptors

Reference Chemicals Working Group

- EPA requested ICCVAM form an interagency working group to:
  - Provide expertise in creating a list of reference chemicals for the evaluation of alternative test methods and testing strategies for identifying potential androgen receptor (AR) agonists or antagonists.
  - List of chemicals should have well-characterized bioactivity (in vitro and in vivo) in the androgen signaling pathway.
- The workgroup will recommend separate lists of *in vivo* and *in vitro* reference chemicals for the evaluation of AR agonist and/or antagonist activity.
- The lists and supporting documentation will be made available to the public and also be submitted to OECD to facilitate international harmonization of test method evaluations.
- Data from the ToxCast and Tox21 programs will be utilized extensively

Priority Area: Biologics Testing

- Botulinum neurotoxin (BoNT)
- ELISA method is currently used by the Food Emergency Response Network to identify foodborne BoNT serotypes, but there are problems:
  - Finite quantities of critical assay reagents
  - Inability to detect all relevant serotypes
  - Inability to discriminate active and inactive BoNT
- FDA-CFSAN requested ICCVAM form an interagency working group to:
  - Identify non-animal alternatives that can fulfill BoNT testing requirements
  - Provide technical input on validation study design and evaluation for identified methods



Communications

- Communities of Practice webinar in January, 2015
  - Developing reverse toxicokinetic models to correlate *in vitro* and *in vivo* activity
  - Well attended via webinar
- ICCVAM Public Forum in May 2015
  - NIH, Natcher Conference Center, Bethesda, MD
  - Over 30 attendees in person; ~100 via webcast
- Updated ICCVAM committee operating procedures and communicated them to stakeholders (completed)
- Outreach to other US agencies (e.g., National Institute of Standards and Technology)

2016 Meetings and Workshop Planned

- Communities of Practice
  - January 2016
- *In Vitro* to *In Vivo* Extrapolation for High Throughput Prioritization and Risk Decision Management
  - February 17-18, 2016, Research Triangle Park, NC
- ICCVAM Public Forum
  - May 2016

Disseminating Information

National Toxicology Program
U.S. Department of Health and Human Services

NICEATM News - August 25, 2015

In this Newsletter:

NIH Presents Conference for Small Business Grant Applicants

New OECD Test Guidelines Available

FDA Seeking Public Input Prior to International Meeting

ICCVAM Advisory Committee to Meet

FutureTox III Conference Planned for November; Abstract Submission Open

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 short to intermediate term (1-5 years) scientific areas that ICCVAM and NICEATM should consider pursuing.
- Please comment on whether current communication efforts are adequate for keeping interested stakeholders informed about ICCVAM activities. Please suggest any other communication efforts that ICCVAM might consider.
- How can ICCVAM better utilize social media to communicate with stakeholders and public?