Updated ICCVAM Goals for FY2015

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Priority Area: Acute Toxicity Testing

• FY 2015 Goals:
  
  – Finalize statistical analysis of the relative contribution of data from acute oral and dermal toxicity tests to pesticide hazard classification and labelling
  
  – Initiate projects related to reducing use of laboratory animal testing for the assessment of acute inhalation toxicity
  
  – Assist federal agency efforts to implement alternative assays related to eye irritation, skin irritation, and skin corrosion
Priority Areas: Skin Sensitization

• Fostering the evaluation and promotion of alternative test methods for skin sensitization has been one of ICCVAM’s long-standing priorities.

• Promise for the near-term development of testing strategies that do not require the use of animals:
  – AOP for skin sensitization is well characterized
  – Number of non-animal test methods have been developed.

• FY 2015 Goals:
  – Continue providing expertise in the design and examination of the predictive value of a battery of *in vitro* and *in silico* methods
  – Evaluate a variety of approach(es) for integrating data from available non-animal methods to use in a prospective evaluation
Non-animal Methods for Skin Sensitisation: Aligned to AOP Key Events

1. Skin Penetration
2. Electrophilic substance: Directly or via auto-oxidation or metabolism

In silico Toxicokinetic model [Kasting; Univ. Cincinnati]
Q (SAR)s [Various]

3-4. Haptenation: Covalent modification of epidermal proteins
5-6. Activation of epidermal keratinocytes & Dendritic cells
7. Presentation of haptenated protein by Dendritic cell resulting in activation & proliferation of specific T cells
8-11. Allergic Contact Dermatitis: Epidermal inflammation following re-exposure to substance due to T cell-mediated cell death

DPRA PPRA [P&G]
AREc322 [CXR Bio.]
KeratinoSens [Givaudan]
LuSens [BASF]
Sensi-DERM [Proteome Sciences]
SENS-IS [Immunosearch]
SensCeeTox [CeeTox]
NCTC 2544 IL-18 [Corsini; Univ. Milan]
Tiered testing approach [Corsini/Gibbs; Univ. Milan/VUMC]
VITOSens [VITO]
h-CLAT [KAO/Shiseido]
mMUSST [BASF]
MUSST [L’Oreal]
PBMD [Beiersdorf]
GARD [Borrebaeck; Univ. Lund]

Human T cell priming [Martin; Univ. Frieburg]
Human T cell proliferation (hTCPA) [Nicholas; Univ. Lyon]

Slide courtesy of Gavin Maxwell (Unilever/Cosmetics Europe)
Chemical Database

- DPRA, KeratinoSens, and h-CLAT data for 120 chemicals from published sources
  - Performed read-across predictions of sensitizer/nonsensitizer outcomes using OECD QSAR Toolbox
  - Collected physicochemical property data
    - Molecular weight
    - Octanol:water partition coefficient
    - Vapor pressure
    - Water solubility
    - Melting Point
    - Boiling Point
Skin Sensitization

- 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)

- “Decision tree” approach

- Analysis submitted to OECD as an IATA case study skin sensitization & peer review manuscript in development.
Example Model: Skin Sensitization

SVM with h-CLAT + OECD + 6 PhysChem Properties

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- Specificity %: 96.2
- Sensitivity %: 97.1
- Accuracy %: 96.8
- Specificity %: 100
- Sensitivity %: 94.7
- Accuracy %: 96.2

• Conclusion: machine learning models are superior to individual assay methods or battery, and achieve better balance between sensitivity and specificity.
Priority Area: Alternatives to HIST Vaccines

• FY 2015 Goal:

  – International working group on implementing *in vitro* assays as alternatives to the murine histamine sensitization test (HIST) for the testing of acellular pertussis vaccines
Communications Plans

• FY 2015 Goals:
  – Convened a Communities of Practice webinar in January, 2015
    • Developing reverse toxicokinetic models to correlate *in vitro* and *in vivo* activity
  – Convene an ICCVAM Public Forum (today)
  – Serve as a forum for communicating an agency position on test method recommendations
  – Serve as a forum for communicating how agencies are implementing the 3Rs
  – Update ICCVAM committee operating procedures and communicate them to stakeholders (completed)