Skin Sensitization Update

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Skin Sensitization

"Allergic Contact Dermatitis"

Accounts for 10-15% of all occupational disease *(Anderson et al. 2010)*

Major testing requirement for cosmetics, pesticides, industrial chemicals, etc.

Accuracy Against Human Clinical Data (~150 chems)

LLNA	GPMT / Buehler

Hazard	Potency	Hazard	Potency
72%-82%	54% - 60%	~72%	~60%

Reproducibility of Multiple Tests (~100 chems)

Hazard	Potency
~78%	~62%

ICCVAM. 1999. NIH Publication No. 99-4494
ICCVAM. 2010. NIH Publication No. 11-7709
Urbisch et al. 2015. Reg Tox Pharm 71:337-351.
Dumont et al. 2016. Tox In Vitro 34: 220-228
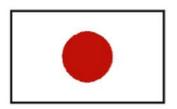Kleinstreuer et al. 2017 in preparation

International Cooperation on Alternative Test Methods (ICATM)

- First ever ICATM Workshop: "International regulatory applicability and acceptance of alternative non-animal approaches to skin sensitization assessment of chemicals used in a variety of sectors"
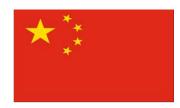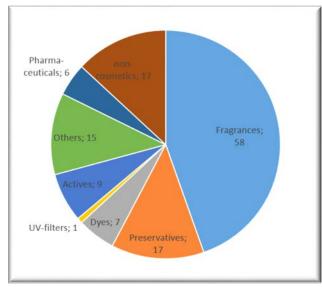
ICATM Workshop Objectives

- Facilitate a common understanding of the available non-animal approaches

- Identify the current regulatory requirements for skin sensitization in different regions that could be satisfied with non-animal approaches

- Identify obstacles to regulatory acceptance of alternative approaches and strategies to resolve them

- Define a set of performance based criteria for regulatory use of defined approaches

- Issue recommendations for specific regulatory applications in defined chemical sectors

Global Skin Sensitization Project

- Objective: analysis of available non-animal approaches

  – OECD submitted testing strategies

- Collaboration with Cosmetics Europe

  – 128 substance dataset

  – LLNA (mouse) and human data

  – Curation/generation of

    - *in vitro* cell-based data that maps to AOP

    - *in silico* computer predictions, chemical structural features & properties
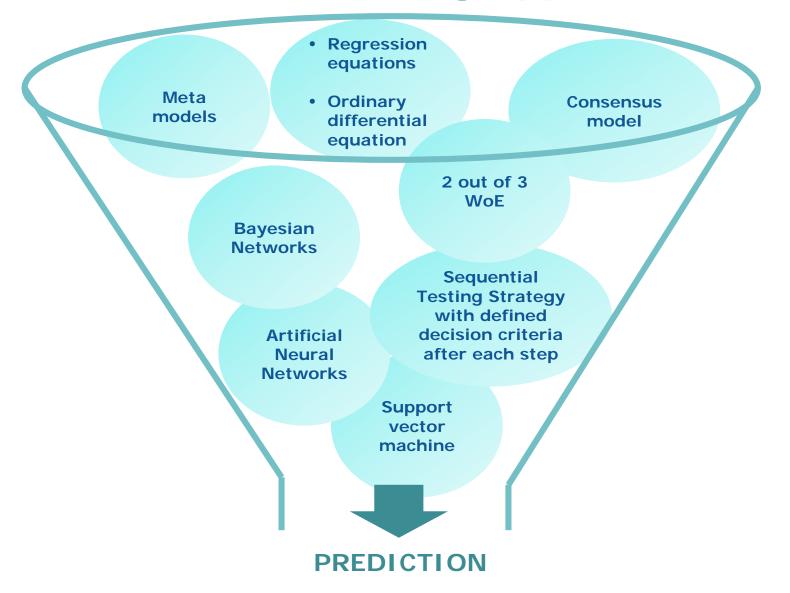

Spectrum of 128 substances
(largely cosmetic ingredients)

- Analyze OECD-submitted approaches (i.e., code packages); open source and transparent (R, Python)

- Evaluate performance against the mouse and human hazard/potency categories

Different Modeling Approaches

- Meta models
- Regression equations
- Ordinary differential equation
- Consensus model
- 2 out of 3 WoE
- Bayesian Networks
- Sequential Testing Strategy with defined decision criteria after each step
- Artificial Neural Networks
- Support vector machine

PREDICTION

Non-Animal Approach Evaluation

Most non-animal testing strategies evaluated so far perform **better** than the mouse test at predicting human skin sensitization hazard and potency.

(And when compared to the mouse data, are equivalent in performance to the mouse at predicting itself.)

International Harmonization

- OECD proposal submitted November 2016

  - Co-led by U.S., EU, and Canada

  - Create an international performance based test guideline for non-animal skin sensitization testing strategies

  - Achieve widespread replacement of mouse test

- Comments from OECD member countries received January 2017, revised proposal submitted March 2017

- National coordinators from 35 member countries voted unanimously to approve the project on April 27, 2017

Expanding Chemical Space Coverage

- Prospective *in vitro* testing supported by NTP (D. Germolec)
- 242 chemicals nominated from NTP, EPA, CPSC
  - Pesticides, industrial chemicals, etc.
- NTP Contractor: Burleson Research Technologies (BRT) running 3 *in vitro* non-animal tests:
  - LuSens (me-too method under OECD TG442D)
  - DPRA (OECD TG442C)
  - h-CLAT (OECD TG442E)
- Screening of 47 chemicals underway in the LuSens assay
  - h-CLAT and DPRA studies will begin in June 2017
- Procurement of additional test chemicals is ongoing
- Results will expand defined approach evaluations

Skin Sensitization Data Collection: Ongoing Efforts

- Multiple conventional & antimicrobial registrants have kindly provided data to support our skin sensitization efforts.

- We continue to collect additional, voluntary data to expand current datasets:

  - Paired *in vitro* & LLNA data that could increase coverage of various defined approaches

  - Other LLNA studies to help assess variability

  - Additional human data to assist in evaluating defined approaches