RIFM Update: Non-Animal Alternatives for Assessing Dermal Sensitization Potency

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DST = Threshold of Toxicological Concern (TTC) for skin sensitization

- Identifies an exposure below which there is a low concern for the induction of sensitization
- Allows for waving testing and/or priority setting
- R Safford developed DST for non-reactive chemicals
  - Safford, 2008, Reg Tox Pharm, 51(2), 195-200.
  - Safford et al., 2011, Reg Tox Pharm, 60(2), 218-224.
- RIFM collaborated with R Safford and D Roberts to develop DST for reactive chemicals and identify high potency chemicals
  - Roberts, et al, 2015. Reg Tox Pharm, 72, 683-693.
  - Safford, R.J., et al 2015. Reg Tox Pharm, 72, 694-701

Animal Alternatives

- More than *in vitro* tests
  - In silico models
  - Consider physical chemical parameters
  - Chemistry
  - Reactivity
  - Data on read across materials
  - Data in cluster of chemicals

RIFM In Vitro Sensitization Research

- Cosmetics Europe Skin Tolerance Task Force
  - Partner on next generation alternatives and models
  - Data generated and gathered on 49 materials in three leading in vitro methods (DPRA, KeratinoSens and hCLAT)
  - Evaluated data in two leading hazard and potency models
- Use a Bayesian Network
  - computer model that combines different data types using
  - probabilistic analyses to predict potency
  - Some advantages to this approach
    - 1) Indicates if there are sufficient data to make a potency prediction
    - 2) If not, can provide a guide to what data are needed

- Jaworska, J., Dancik, Y., Kern, P., Gerberick, F., Natsch, A., 2013 Journal of Applied Toxicology and Pharmacology 33, 1353
- ITS-3 was published late last year—Jaworska, J, Natsch, A., Ryan, C., Strickland, J., Ashikaga, T., Miyazawa, M., Archives of Toxicology December 2015, Volume 89, Issue 12, pp 2355-2383

Potency Prediction in the Bayesian Network

- Model currently define 4 potency classes (None, Weak, Moderate and Strong)
- Results of analyzing the RIFM dataset:
  - Dataset focused on weak and moderate fragrance sensitizers
  - Hazard prediction - Very good 96%
  - Weak Sensitizers - Good predictions 74% (Comparable to LLNA)
  - Moderate Sensitizers - Low predictivity 38% (Small sample size, overall one class away)
  - Additional analysis needed to strengthen relevance for weak sensitizers and increase prediction of moderate sensitizers

Potency Prediction in the Bayesian Network

- Further analysis is required to improve potency predictions
- Bayesian Network ITS continues to show promise for decision support
  - i.e. Even today, a weak potency classification could allow us to move human confirmatory studies and avoid lower default QRA restrictions.
- Similar results with neural network model
  - Verification of a skin sensitization assessment neural network model by fragrance materials. T.Atobe, M.Hirota, T.Ashikaga, A.M.Api and J.F.Lalko. Society of Toxicology 54th Annual Meeting, March 22-26, 2015, San Diego, CA, USA.

Potency Prediction in the Bayesian Network

- Based on the outcome of the potency prediction analysis and follow-up, determine next materials for data generation
- *These predictions were done when ITS-3 was still under development. They could be different from finalized version of ITS-3 published late last year.
  - LogDpH7, fraction ionized and WsPH7 were not used. Instead, like ITS-2 we used LogKow, Cfree, AUC 120% for bioavailability

RIFM In Vitro Sensitization Research

- **In-vitro assays**
  - **RIFM-CE collaboration (2013)**
    - **49 materials have been tested in DPRA, KeratinoSens™, hCLAT and/or U-Sens™**
  - **RIFM Research (2015)**
    - **PPRA and Sens-IS® have been added to the in-vitro battery**
    - **50 new materials will be tested in all 6 assays**
  - **Analyze data in finalized version of ITS-3**