Poster
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Cosmetics Europe Assessment of Non-Animal Approaches for Predicting Skin Sensitization

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Abstract

Skin sensitization is a toxicity endpoint of widespread concern, for which non-animal testing approaches are available. Cosmetics Europe and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods analysed the performance of multiple non-animal data integration approaches for the skin sensitization safety assessment. We collected and generated data on 128 substances in multiple in vitro and in chemico skin sensitization assays which are key components of various non-animal defined approaches to testing and assessment that have been submitted to the OECD as case studies for skin sensitization. LLNA and human sensitization data were used to evaluate the performance of multiple non-animal testing strategies for hazard and potency characterization. Defined approaches examined include consensus methods, artificial neural networks, support vector machine models and decision tree, all of which were reproduced using open source software tools.

Introduction

Cosmetics Europe's Skin Tolerance Task Force's aim is to provide regulatory accepted non-animal test strategies that enable cosmetic industries to conduct skin sensitization safety assessments.

To reach this aim, a program of four phases has been devised. In Phase I, 16 individual test methods were evaluated in detail, prioritising six test methods. Data for 128 substances tested in these methods were compiled in a database in addition to curated results of LLNA and human potency categories. We evaluated the predictivity of six defined approaches (DA):-BASF '2 out of 3', ICCVAM SVM, KAO STS and ITS, P&G BN ITS, Shiseido ANN. Multiple non-animal testing strategies incorporating *in vitro*, *in chemico*, and *in silico* inputs demonstrated comparable or superior accuracy to the LLNA when the prediction was compared to either animal or human data for skin sensitization. We propose our database and the open source software tools as a point of reference for the evaluation and development of DA and encourage the community to use it to meet the challenge of conducting skin sensitisation safety assessment without generating new animal data.

Project overview and results

Phase I

Method Identification & Prioritisation

Systematic evaluation of 16 test methods using predefined criteria and data on 10 substances Detailed understanding allowed prioritisation of six test methods covering key events of AOP

Prioritised: DPRA, U-SENS, KeratinoSens™, SENS-IS, h-CLAT, PPRA (ongoing)


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Systematic evaluation of non-animal test methods for skin sensitisation safety assessment

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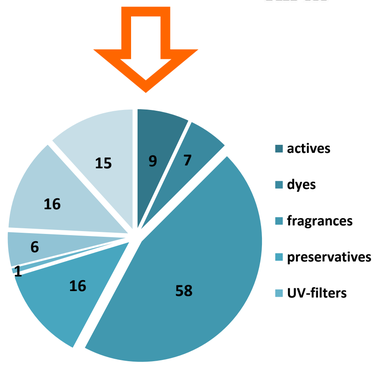
Phase II- description

Data Collection, Generation and Compilation

1. **Substance selection**
   - **98 substances from Basketter et al., 2014**
   - **human data available and categorised**
   - **LLNA data available**
   - **30 fragrances in collaboration with RIFM (human and LLNA data available)**



2. **Data collection**
   - **all existing primary output data of 6 test methods for the 128 substances**
   - **all existing LLNA data fulfilling quality criteria (curated by ILS)**
3. **Data generation**
   - **blinded testing to fill data gaps for the 6 test methods**
   - **quality checked**
   - **assignment of human categories for RIFM set**
4. **Data compilation**
   - **storage of all data in ambit database**
   - **public access planned**

Assessment of Testing Strategies

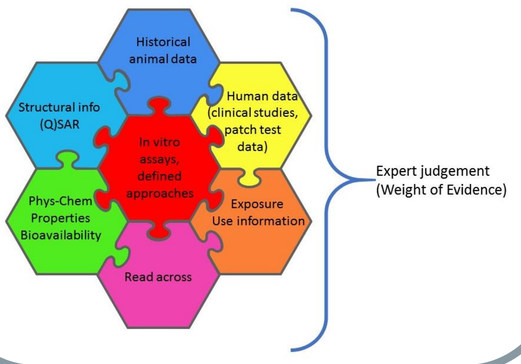
1. **Qualitative characterisation of 12 skin sensitisation DA/IATA case studies against defined criteria**
2. **Evaluation of the predictive performance of six DA/IATA case studies using database**
   - **reproduced algorithms**
   - **independent assessment with the same sets of reference data**

BASF	'2 out of 3' approach
ICCVAM	Support Vector Machine (SVM) approach
Kao ITS	Score-based battery system
Kao STS	Sequential Testing Strategy
P&G	Bayesian Network Integrated Testing Strategy (ITS)
Shiseido	Artificial Neural Network for predicting LLNA EC3

DuPont	Implementation of an IATA into a pipeline tool (IATA-SS)
Givaudan	Data from KeratinoSens and Kinetic Peptide Binding: Global Versus Domain-Based Assessment
L'Oréal	L'Oreal's decision strategy using a "staking" meta-model
RIVM	RIVM Sequential Testing Strategy
Unilever	IATA for Skin Sensitisation Risk Assessment
JRC	Consensus of classification trees

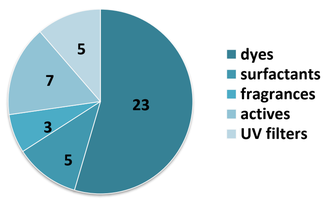
Phase IV

Risk assessment case studies for cosmetic ingredients



OBJECTIVE
Skin sensitization risk assessment of cosmetic ingredients
- **without animal testing**
- **accepted by regulators**

Phase III



Distribution of chemicals selected for phase III

Assessment of applicability domains

Blinded testing (blind) of 43 challenging substances of high importance for cosmetic industry

Optimisation of DA

- amend existing DAs providing potency information
- explore the use of SENS-IS and PPRA in DAs

Phase II- results

Comparison of human and LLNA reference data

6 DA were assessed for prediction of sensitisation hazard & potency prediction:
- defined approaches vary in complexity and required resources
- provide comparable or superior performance to the LLNA compared to human data

- Propose our database and open source software tools as a point of reference for the scientific community

DA assessment: hazard ID

Predicting Human Hazard								
Defined Approach:	BASF 2/3 (DKH)	Kao STS	Kao ITS	ICCVAM SVM (Human)	Shiseido ANN (D_hC)	Shiseido ANN (D_hC_KS)	P&G BN ITS-3	LLNA
N	127	126	120	120	126	126	119	128
Accuracy (%)*	77.2	80.2	85.0	81.7	78.6	78.6	75.6	74.2
Sensitivity (%)	79.3	97.7	93.8	86.4	95.4	100	81.3	85.2
Specificity (%)	72.5	41.0	66.7	71.8	41.0	30.8	64.1	50.0

Predicting LLNA Hazard							
Defined Approach:	BASF 2/3 (DKH)	Kao STS	Kao ITS	ICCVAM SVM (LLNA)	Shiseido ANN (D_hC)	Shiseido ANN (D_hC_KS)	P&G BN ITS-3
N	127	126	120	120	126	126	119
Accuracy (%)*	70.1	77.8	79.2	84.2	76.2	81.0	83.2
Sensitivity (%)	72.3	92.6	85.6	86.7	90.4	97.9	83.2
Specificity (%)	63.6	34.4	60.0	76.7	34.4	31.3	83.3

DA assessment: potency prediction*

Predicting Human Potency (Strong, Weak, Non sensitizers)						
Defined Approach:	Kao STS	Kao ITS	Shiseido ANN (D_hC)	Shiseido ANN (D_hC_KS)	P&G BN ITS-3	LLNA
N	126	120	126	126	115	128
Accuracy (%)*	63.5	69.2	61.1	62.7	54.8	59.4
Overpredicted (%)	22.2	13.3	22.2	25.4	20.0	19.5
Underpredicted (%)	14.3	17.5	16.7	11.9	25.2	21.1

Predicting LLNA Potency (Strong, Weak, Non sensitizers)					
Defined Approach:	Kao STS	Kao ITS	Shiseido ANN (D_hC)	Shiseido ANN (D_hC_KS)	P&G BN ITS-3
N	126	120	126	126	115
Accuracy (%)*	67.5	66.7	65.1	69.8	67.8
Overpredicted (%)	21.4	14.2	21.4	23.0	12.2
Underpredicted (%)	11.1	19.2	13.5	7.1	20.0

*3-classes: strong, weak and NS

This work was sponsored by Cosmetics Europe

References: Basketter et al. (2014). Categorization of chemicals according to their relative human skin sensitizing potency. Dermatitis 25(1):11-21.
Reisinger et al. (2015). Systematic evaluation of non-animal test methods for skin sensitisation safety assessment. Toxicology in vitro 29(1):259-70.