



Interagency Coordinating Committee on the Validation of Alternative Methods

NICEATM Skin Sensitization Projects

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SACATM Meeting
September 24, 2013
National Institute of Environmental Health Sciences
Durham, North Carolina

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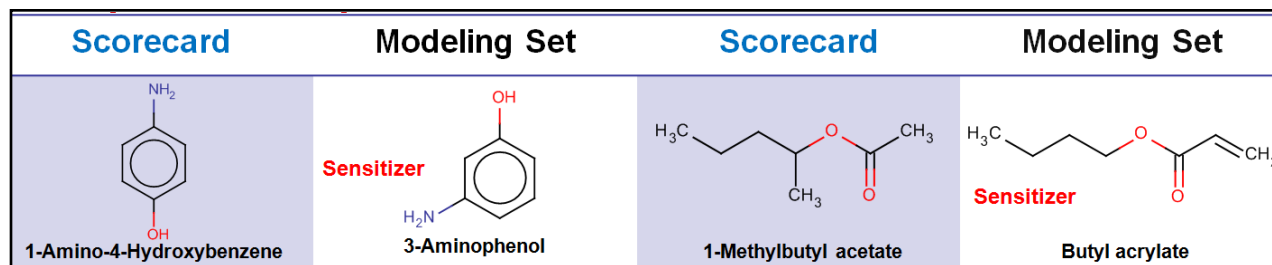
NICEATM Efforts: Skin Sensitization

3 R's

- Collaborations to develop and evaluate chemical structure-activity relationship (SAR) models for predicting skin sensitization
- Develop an open-source Bayesian network that uses multiple physicochemical, *in silico*, *in chemico*, and *in vitro* inputs to predict skin sensitization
- Coordinate with the OECD AOP program for skin sensitization to guide development of an integrated testing strategy (ITS)
- Evaluate high throughput screening (HTS) assays from ToxCast/Tox21 program for relevance to skin sensitization

QSAR Model of Skin Sensitization

- After NICEATM data curation, 262 compounds retained for modeling (multiple 2D chemical descriptors and Random Forests)
 - 134 sensitizers and 128 non-sensitizers
 - Consensus model (75% coverage): 80% BA (5-fold cross val.)
- External validation on Scorecard dataset using QSAR models and similarity search



- Benchmarking with OECD QSAR Toolbox on 153 external compounds

	Sensitivity	Specificity	Coverage
Consensus	73%	91%	84%
OECD Toolbox	69%	20%	97%

Creating an Open Source Model for Probabilistic Skin Sensitization Hazard Prediction

Journal of
Applied Toxicology

Research Article

Received: 14 January 2013,

Revised: 4 February 2013,

Accepted: 4 February 2013

Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/jat.2869

Bayesian integrated testing strategy to assess skin sensitization potency: from theory to practice

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ABSTRACT: Frameworks to predict *in vivo* effects by integration of *in vitro*, *in silico* and *in chemico* information using mechanistic insight are needed to meet the challenges of 21st century toxicology. Expert-based approaches that qualitatively integrate multifaceted data are practiced under the term 'weight of evidence'. Quantitative approaches remain rare. To address this gap we previously developed a methodology for Bayesian Integrated Testing Strategy (ITS) in the form of a Bayesian Network (BN). This study follows up on our proof of concept study. The updated ITS presents an updated ITS to assess skin sensitization

Open source software



<http://www.r-project.org/>

Bayesian Networks (BNs):

- Probabilistic graphical models
- Can be used to represent knowledge about a domain of interest and facilitate reasoning involving uncertain evidence

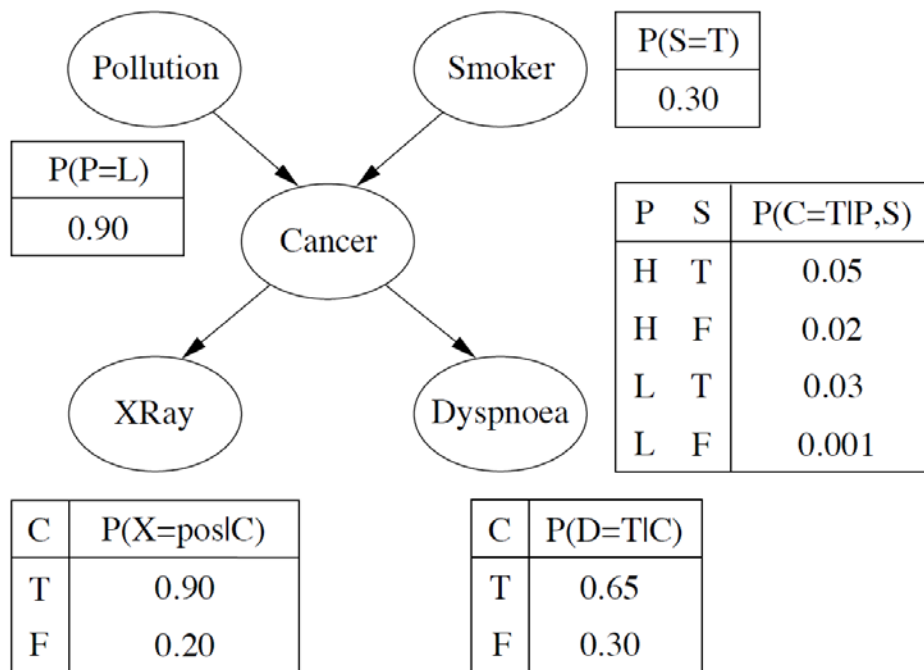


Figure 1. Simple Lung Cancer BN

Korb and Nicholson. 2010

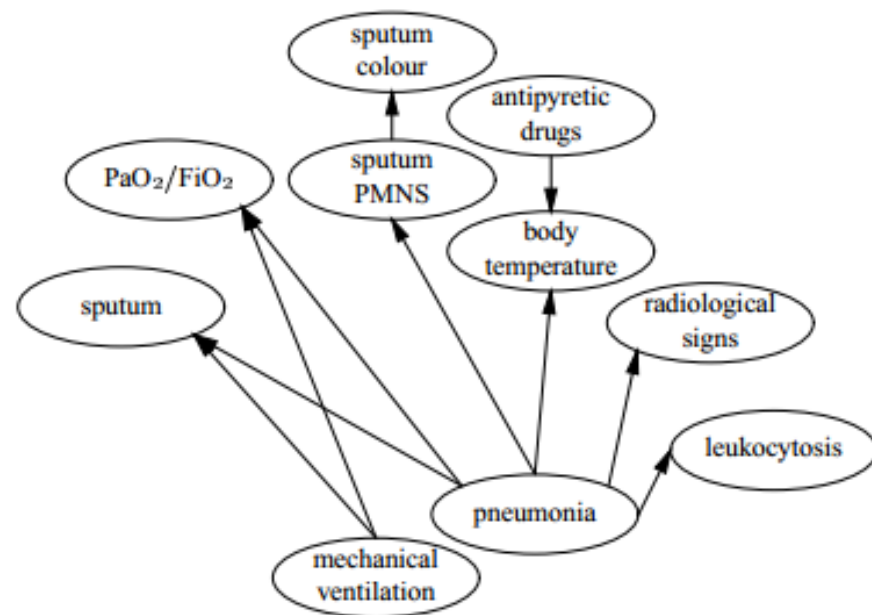
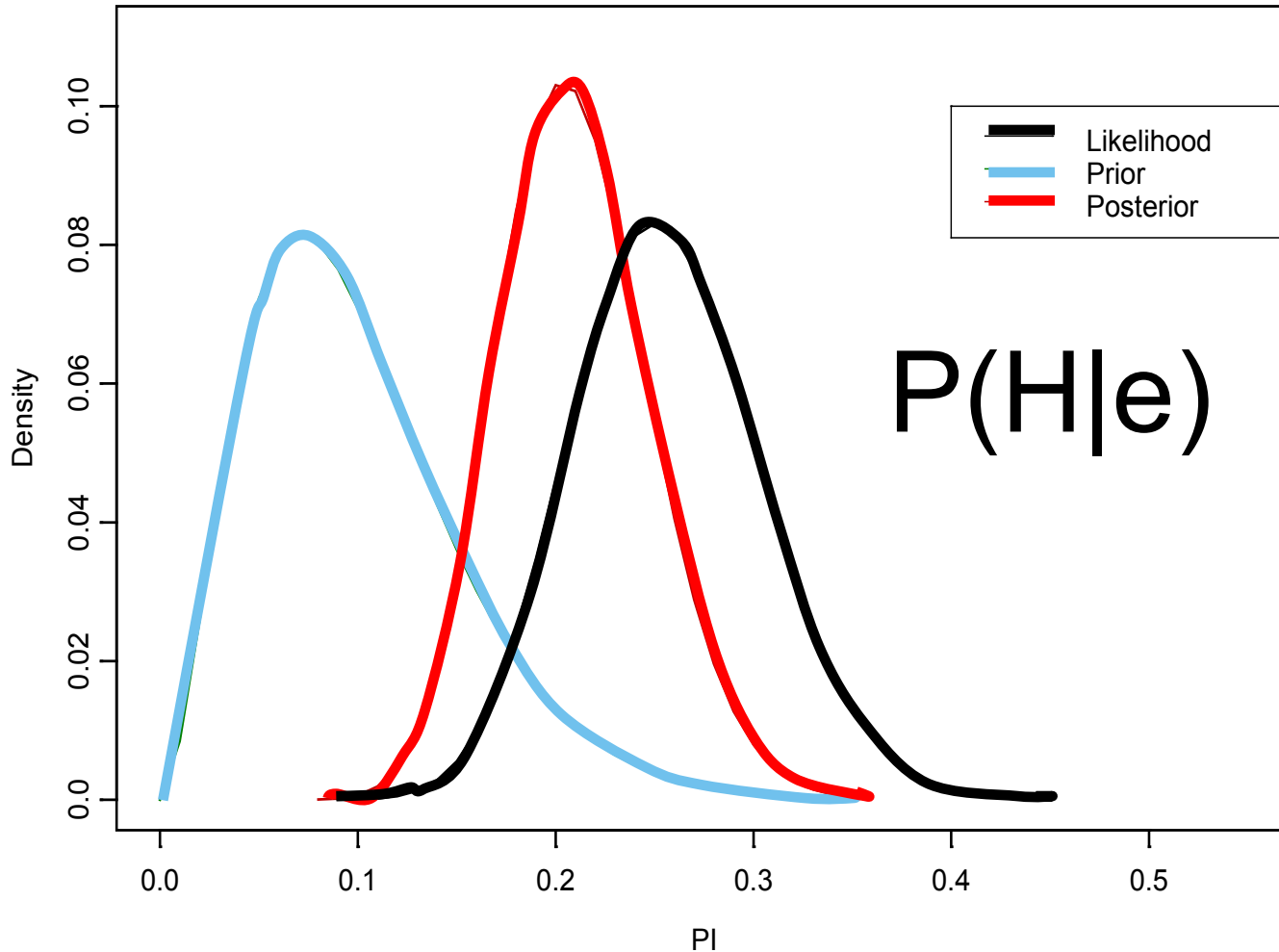


Figure 2. BN of Signs and Symptoms of Pneumonia

Charitos et al. 2007

Hypothesis (prior) X Evidence (likelihood) = Revised Hypothesis (posterior)

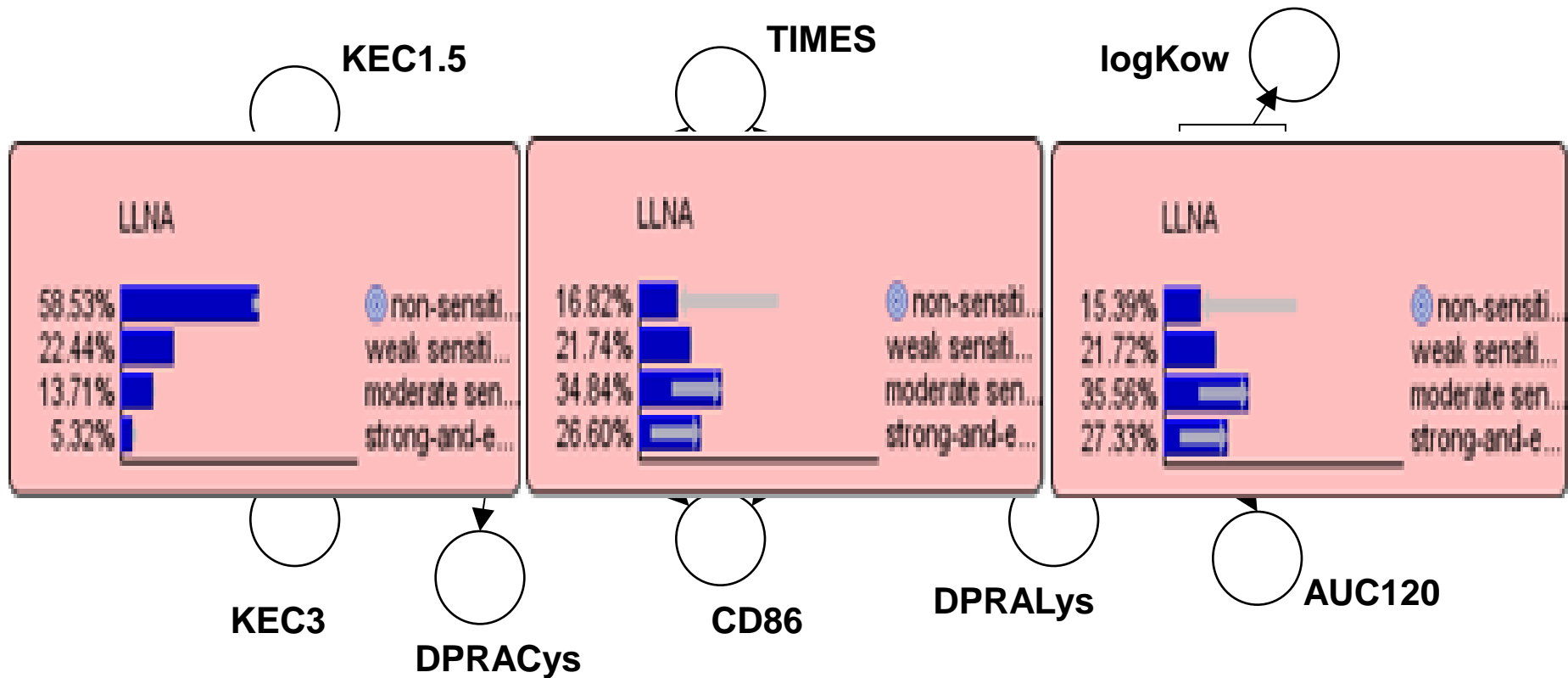
Example of Bayes' Theorem



Jaworska et al. 2013

ITS-2

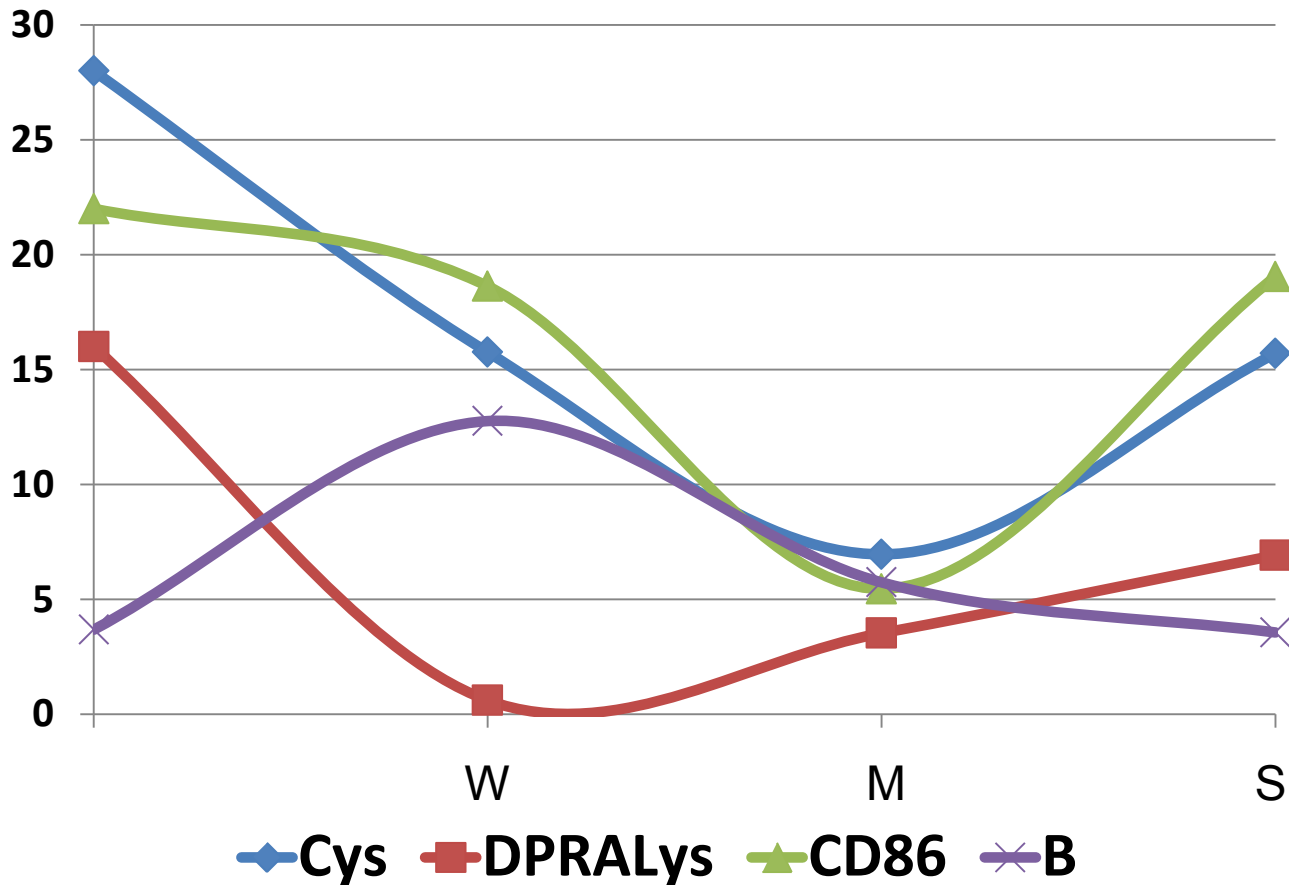
P(LLNA=NS, W, M, S | evidence)



Data set n=145: Training set n=121, Test set n=21 7

Mutual Information

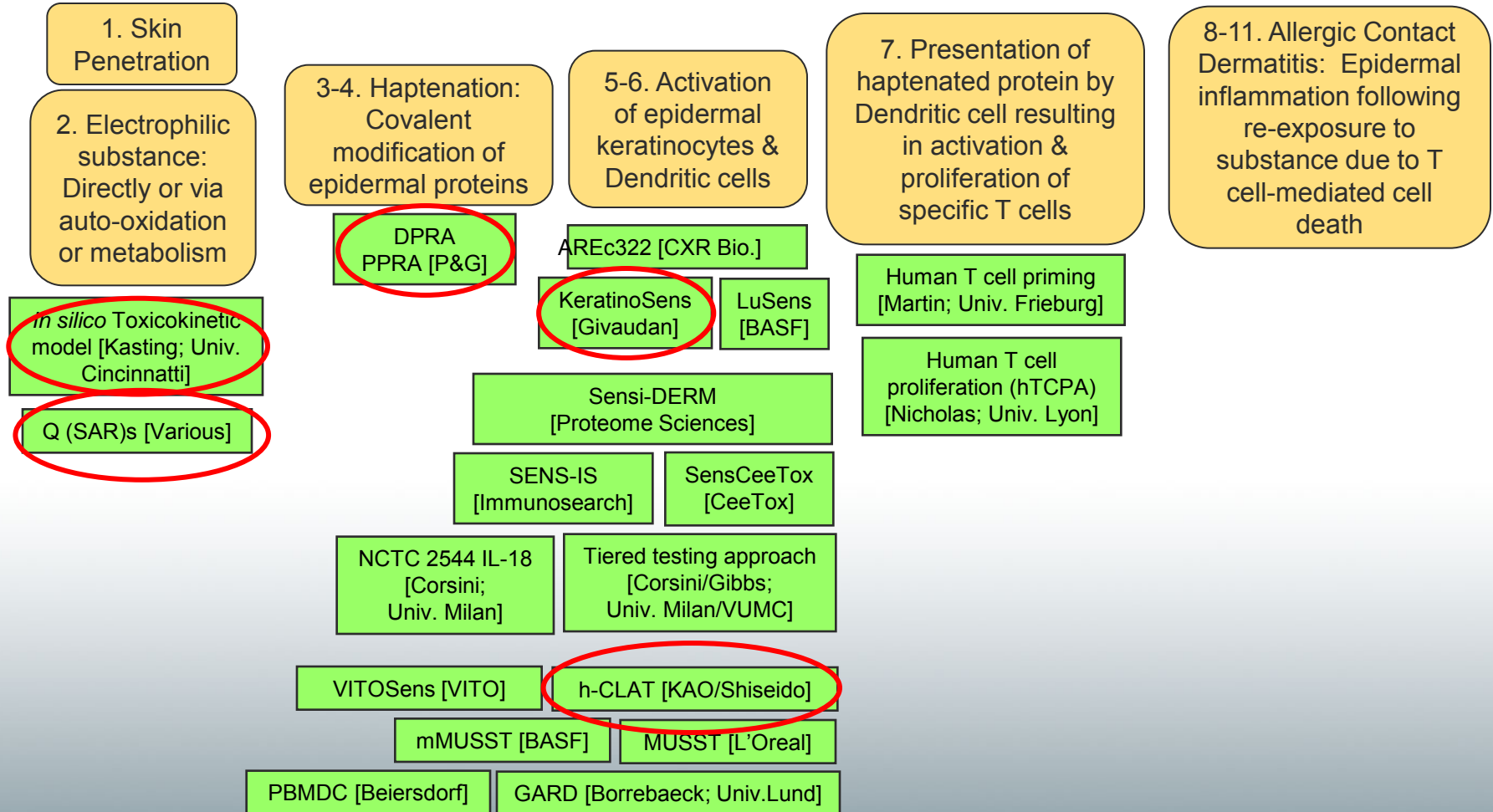
Assays that Help Predict LLNA Potency Class



Non-animal Methods for Skin Sensitisation: Aligned to AOP Key Events

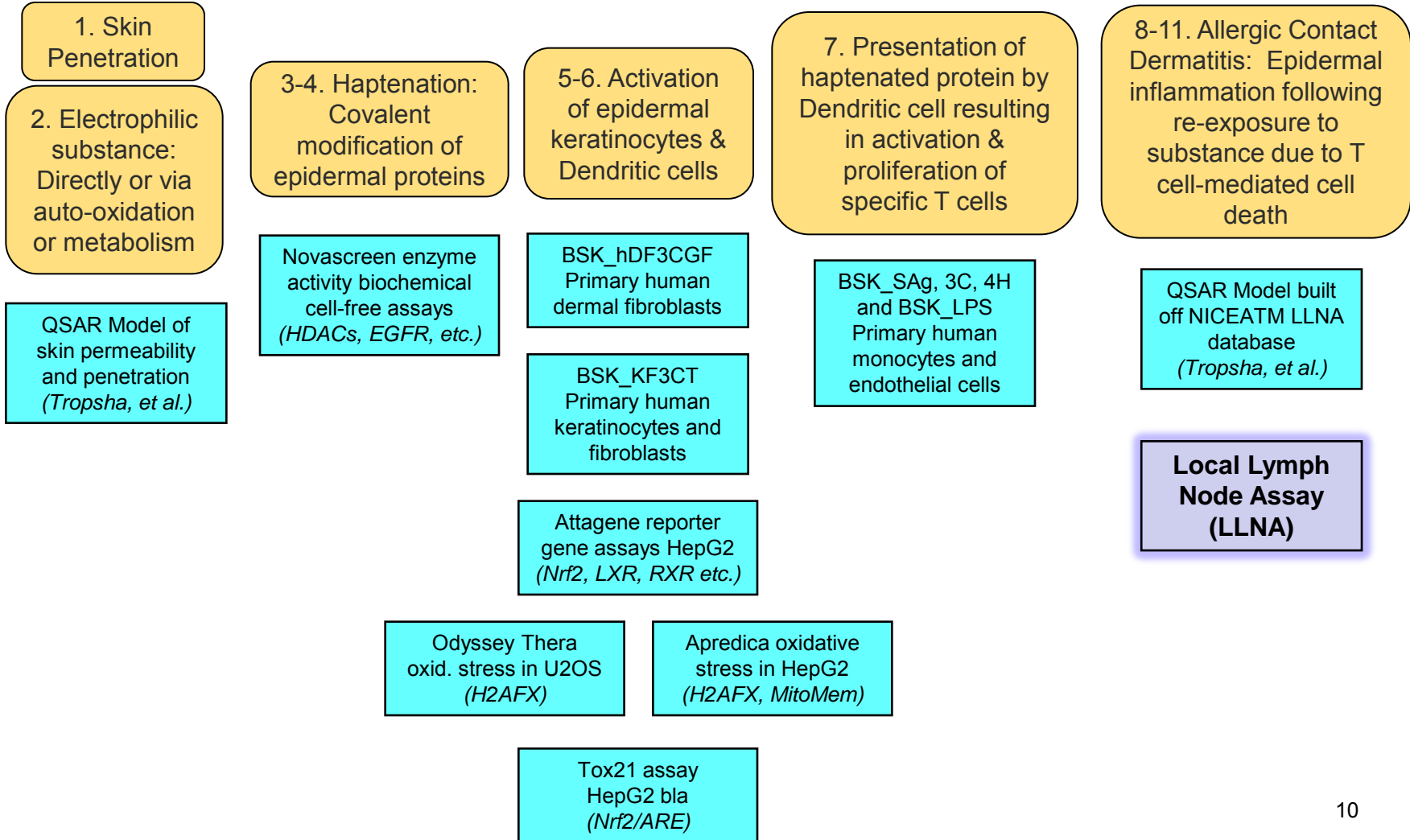


Cosmetics Europe
the personal care association



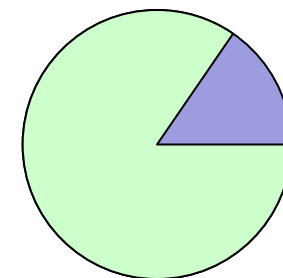
Slide courtesy of Gavin Maxwell (Unilever/Cosmetics Europe)

Tox21 Assays: Aligned to AOP Key Events



Random Forest Model for predicting LLNA with ToxCast *in vitro* HTS data: 5-fold Cross Validation (n=64 chemicals)

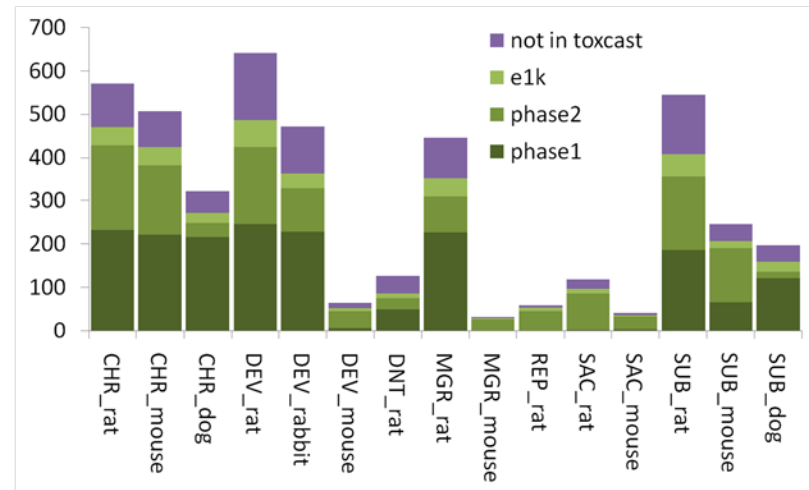
Model Run	Assay 1	Assay 2	BA
1	Primary human dermal fibroblasts Collagen III Proliferation	Activated monocytes Prostaglandin IL-8	0.92
2			0.94
3	Transactivation assays Nrf2/ARE RXRb	Oxidative Stress Mitochondrial membrane potential	0.69
4			0.67
5			0.76
AVG	Assay targets that map to AOP		0.79



80% Training Set
20% Test Set

Expand ToxRefDB: *in vivo* Study Data

- ImmunoTox initiative (led by NTP/NICEATM)
 - Develop ontology for entering study data
 - Including LLNA and other skin sensitization studies
 - Enter NTP/EPA studies first, then open lit search
- Skin sensitization data exist for ALL pesticides
 - NO skin sens data currently in ToxRefDB
 - Studies requested from EPA
 - Via FOIA in 2012
 - Via personal request (May 2013)
 - Recent data evaluation records (DERs) may be available soon



Summary

- NICEATM supports efforts to create probabilistic frameworks for inference and testing strategy development
- Open source ITS Bayesian Network structure that follows mechanistic steps of skin sensitization induction process
 - BN ITS topology and AOP are very similar
 - External validation: 86% correct for potency, 95% for hazard
 - QSAR models under development may improve ITS
- Well characterized AOPs like skin sensitization provide opportunities to use HTS data (ToxCast, Tox21)
 - Mapping *in vitro* assays to AOP based on biological knowledge
 - Building statistical models on training sets using random forest and other multivariate techniques

Acknowledgments

- Warren Casey
- ILS, Inc. / NICEATM
- J. Pirone, M. Smith, R. Morris, SSS
- Joanna Jaworska, P&G
- U.S. EPA ToxCast team
- Tropsha Lab, UNC-CH
- Gavin Maxwell, Unilever
- NIEHS / NTP

Questions?