Assessing skin sensitization potential by combining multiple sources of information in a quantitative weight-of-evidence approach

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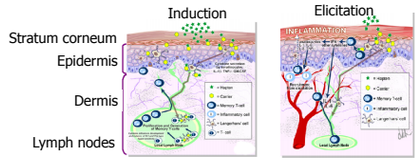
INTRODUCTION

Evaluating chemical toxicity instigated by dermal contact requires addressing exposure (permeation) and chemical reactivity that leads to irritation or subsequent sensitization via well-known induction/elicitation immune response mechanisms:



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Molecular initiating events in sensitization: hapten-protein adduct formation reactions:

Schiff base formers
Aldehyde binding to lysine

Michael acceptors
α,β-unsaturated carbonyl binding to cystein

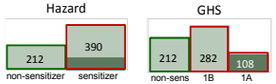
S_NAr
Aromatic nucleophilic substitution

S_N2
e.g. primary-alkyl halides. etc.

Smith Pease, C.K., Toxicology, 192, 2003, 1-22
Aptula, et. al. Chem. Res. Toxicol. 19, 2006, 1097

LLNA TRAINING SET

Distributions of hazard and GHS calls



A total of 602 structures, mostly organic

Hazard: non-sensitizer (0) EC3 not calculable or EC3 > 100 %
GHS: non-sensitizer (0); EC3 > 2 % (1B); EC3 ≤ 2 % (1A)

Chemical-protein reactivity classes in training set that discriminate potency

Mechanistic category	compound classes	Z-score	N
Nitrenium ion formation	aromatic amine	4.49	83
SN Ar	armoatic nitro w/ e-withdrawing group	3.22	42
Alkylating agent	acyl halide + acid anhydride	3.21	14
Pro-miachel acceptors	phenol	2.19	81
Michael acceptors	a,b-unsaturated aldehyde, ketone, nitrile, nitro	0.61	52
Schiff base formers	aldehydes and ketones	-0.38	129
SN2	aliphatic halide	0.30	55
	aliphatic alcohol	-4.70	101
	all alcohol	-2.61	171

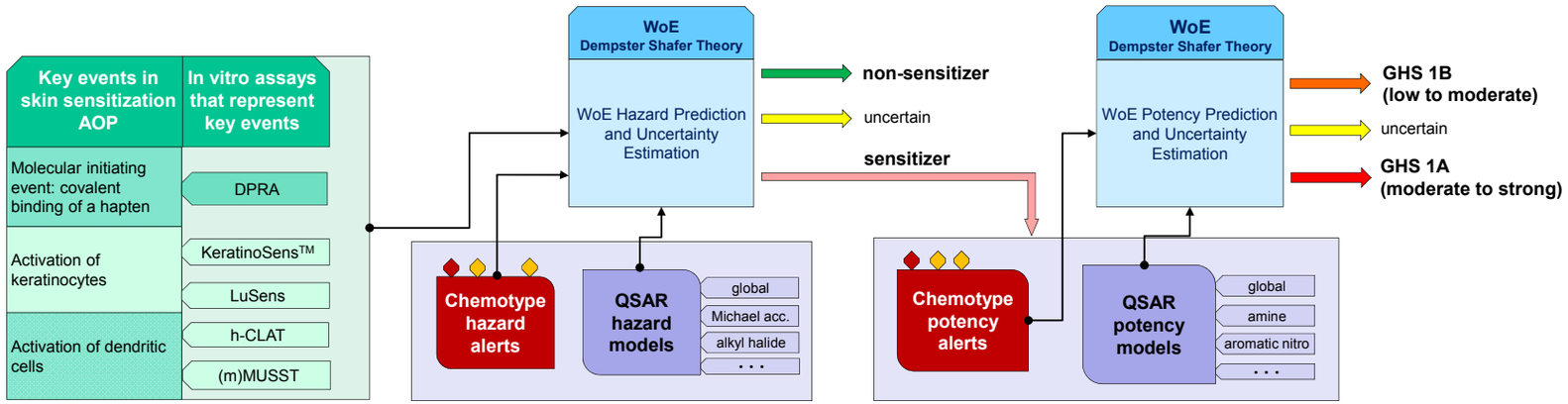
Partial list of influential descriptors (global models):

ToxPrint chemotypes[1,2,3]
chain:alkaneLinear_ethyl_C2
bond:CN_amine_aromatic_generic
bond:COH_alcohol_sec-alkyl
chain:alkeneBranch_mono-ene_2-butene
chain:alkaneLinear_propyl_C3
bond:N(=O)_nitro_aromatic
bond:COH_alcohol_aliphatic_generic
bond:C=O_carbonyl_ab-unsaturated_aliphatic
chain:alkaneLinear_butyl_C4
ring:aromatic_benzene
bond:C=O_aldehyde_aromatic

Physicochemical properties
HOMO/LUMO
logP
logS
topological polar surface area (TPSA)
dipole moment
hydrogen bond acceptors and donors complexity
rotatable bonds
diameter

References
[1] Yang C, et. al. *J Chem Inf Model*. 2015 Feb 19. [Epub ahead of print]
[2] http://www.chemotyper.org
[3] http://www.toxprint.org
[4] Urbisch, et al., *Reg Tox and Pharm 71* (2015) 337-351

SKIN SENSITIZATION PREDICITON WORKFLOW



WoE APPROACH

Dempster-Shafer theory (DST) is an extension of Bayesian inference that allows probabilistic estimates to be assigned to sets of events. Key features:

- quantitative estimation of uncertainty
- systematic method of combining evidence sources
- more rigorous and theoretically sound than simplistic consensus WoE approaches
- reliability metrics from cross validation on training data

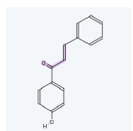
For QSAR models and in vitro assays, positive prediction value (PPV) and negative prediction value (NPV) provide appropriate reliability metrics. For alerts, only PPV is relevant since alerts only generate "positive" predictions.

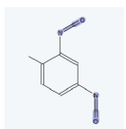
Reliability metrics for hazard

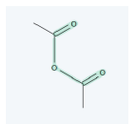
QSAR models	PPV	NPV
Global	0.674	0.686
Michael acceptors	0.846	0.687
Aliphatic halide	0.673	0.733
Alcohol	0.755	0.734
Aliphatic alcohol	0.673	0.773
Aldehydes & ketones	0.834	0.703
Amines	0.873	0.727
Phenol/quinones	0.817	0.628
in vitro Assays[4]	**PPV**	**NPV**
DPRA	0.867	0.568
KeratinoSens™	0.847	0.516
LuSens	0.809	0.600
h-CLAT	0.850	0.566
(m)MUSST	0.862	0.548
Alerts	**PPV**	
carbonyl_ab-unsatur-ated_aliphatic (MA)	0.867	
acyl_halide	0.800	
1,2 di-carbonyl	0.786	
sulfide	0.778	
acid anhydride	0.714	

Reliability metrics for potency

QSAR models	PPV	NPV
Global	0.662	0.736
Amine	0.665	0.701
Aromatic nitro	0.722	0.800
Alerts	**PPV**	
carbonyl_ab-unsatur-ated_aliphatic (MA)	0.720	
epoxide	0.647	
ketone	0.614	


Michael acceptor


isocyanate


acid anhydride


epoxide

Simple examples of skin sensitization alerting chemotypes

RESULTS AND CONCLUSIONS

Skin sensitization hazard prediction performance compared on test set of 138 compounds for which DPRA, KeratinoSens™, and h-CLAT in vitro assay data are available.

Hazard prediction performance	*sensitivity (sensitizer)*	*specificity (non-sensitizer)*	*uncertain*
QSAR	87%	82%	5%
QSAR/alerts	88%	82%	5%
in vitro assays "2 out of 3" approach[4]	79%	77%	N/A
QSAR/alerts/assays	95%	76%	2%

("2 out of 3" approach applied to a set of 180 compounds using data from all five in vitro assays gave 82% sensitivity and 72% specificity.[4])

Skin sensitization potency prediction performance on test set of 99 sensitizers (from the 138-compound set).

Potency prediction performance	*sensitivity (GHS 1A)*	*specificity (GHS 1B)*	*uncertain*
QSAR	83%	83%	12%
QSAR/alerts	85%	81%	10%

Relative to QSAR predictions alone, the number of "uncertain" results for both hazard and potency predictions decreases with the addition of chemical alerts or in vitro assay results.

- ❑ Combination of QSAR and chemical alerts provides good prediction performance for both skin sensitization hazard and potency
- ❑ Combining QSAR, chemical alerts, and in vitro assays for hazard prediction yields excellent sensitivity, but does not significantly improve specificity.
- ❑ Future work will focus on identifying additional discriminating chemical alerts for potency.
- ❑ The current approach of using in vitro assays is helpful for hazard prediction, but not potency. Quantitative assay results (e.g., IC50) will be analyzed to explore whether assays should also be incorporated into potency models to help distinguish between low-to-moderate and moderate-to-strong sensitizers (GHS categories 1B and 1A, respectively).

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