About section of a profiler
Name of the profiler
Protein binding potency Lys (DPRA 13%)
Developer; Donator; date; version
Developer: Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria ***Donator:*** Natsch et al., Urbisch et al., Jaworska et al. ***Version:*** v.01 December 2016
Relevance/Applicability to endpoint(s)
This profile is built in relation with the implementation of the adverse outcome pathway (AOP) for skin sensitization. It is developed on the base of data derived from Direct Peptide Reactivity Assay (DPRA). The DPRA is a reactivity assay which evaluates the ability of chemicals to react with proteins. As model peptides are used reduced glutathione and two synthetic peptides – lysine and cysteine. The reaction time for both lysine and cysteine is 24 hours. The peptide reactivity is reported as percent peptide depletion. The profile contains 73 structural alerts extracted from about 228 chemicals with experimentally measured lysine depletion values. The set of 73 structural alerts are separated into three potency categories: DPRA above 21% (DPRA 13%), DPRA less than 9% (DPRA 13%) and Grey zone 9-21% (DPRA 13%). Classification of potency categories is based on analysis published in collaboration with L`Oreal (Dimitrov et al., 2016).
Relevance/Applicability to particular chemical classes
This profiler is applicable to those organic chemicals that have presence of a functional group reacting with the lysine residue. The presence of an alert is not bounded with parametric ranges; it is based on structural boundaries only.
Approach used to develop the profiler - Concise but informative description of:
a) The aim of the profiler is to investigate the chemicals for presence of functional group able to interact with Lysine peptide and to provide information about the potency of the interaction.
b) The profiler was developed on a basis of experimental data for reactivity toward model peptide measured as percent peptide depletion. The data has been obtained by measuring the covalent binding of the target chemicals with the amino group of lysine (Lys).
c) The profiler was based on a dataset of 228 chemicals with experimental Lys depletion values. A list of 73 structural alerts has been derived. The structural alerts have been separated into three potency categories based on specific peptide depletion ranges. Each alert was associated by a local list of training set chemicals.
d) Literature references: • Gerberick, G.F., Vassallo, J.D., Bailey, R.E., Chaney, J.G., Morrall, S.W. and Lepoittevin, J.P. 2004. Development of a peptide reactivity assay for screening contact allergens. Toxicol. Sci. 81: 332-343. • Natsch, A. and Gfeller, H. 2008. LC-MS-based characterization of the peptide reactivity of chemicals to improve the in vitro prediction of the skin sensitisation potential. Toxicol. Sci. 106: 464-478. • Natsch, A., Emter, R., Gfeller, H., Haupt, T. and Ellis, G. 2015. Predicting skin sensitizer potency based on in vitro data from KeratinoSens and kinetic peptide binding: global versus domain-based assessment. Toxicol. Sci. 143(2), 319-332.

- Jaworska, J., Natsch, A., Ryan, C., Strickland, J., Ashikaga, T., Miyazawa, M. 2015. Bayesian integrated testing strategy (ITS) for skin sensitization potency assessment: a decision support system for quantitative weight of evidence and adaptive testing strategy. Arch Toxicol, 2355-2383.
- Urbisch, D., Mehling, A., Guth, K., Ramirez, T., Honarvar, N., Kolle, S., Landsiedel, R., Jaworska, J., Kern, P., Gerberick, F., Natsch, A., Emter, R., Ashikaga, T., Miyazawa, M., Sakaguchi, H. 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. Regulatory Toxicology and Pharmacology 71: 337-351.
- S. Dimitrov, A. Detroyer, C. Piroird, C. Gomes, J. Eilstein, T. Pauloin, C. Kuseva, H. Ivanova, I. Popova, Y. Karakolev, S. Ringeisses, O. Mekenyan, Accounting for data variability, a key factor in in vivo/in vitro relationships: application to the skin sensitization potency (in vivo LLNA versus in vitro DPRA) example. J Appl Toxicol, 2016, DOI 10.1002/jat.3318

Summary description of profiles/alerts within the profiler

Profile/structural alert	Phys-chem parameter
DPRA above 21% (DPRA 13%)	
Activated 1,3,5-triazine derivatives	No parameter
Allyl glycidyl and benzyl glycidyl ethers (reactive)	No parameter
Aminophenol derivatives (reactive)	No parameter
Benzyl halides	No parameter
Conjugated alpha,beta-unsaturated aldehydes (reactive)	No parameter
Conjugated alpha,beta-unsaturated esters (reactive)	No parameter
Cyclic acid anhydrides	No parameter
Diacylperoxides	No parameter
Halogenated isothiazolone derivatives	No parameter
Hydroxybenzene derivatives and quinones (reactive)	No parameter
Isocyanates and Isothiocyanates	No parameter
Lactones fused to aromatic rings	No parameter
Maleic anhydride derivatives	No parameter
Nitroaniline derivatives	No parameter
Non-alpha,beta-conjugated monoaldehydes (reactive)	No parameter
Non-Conjugated carboxylic acids and esters (reactive)	No parameter
Non-conjugated mono- and diketones (reactive)	No parameter
Oxazolone derivatives	No parameter
Phenylenediamine derivatives (reactive)	No parameter
Saturated dialdehydes	No parameter
Vinylene 1,2-bis-carboxylates	No parameter
DPRA less than 9% (DPRA 13%)	
1,1-Dihaloethenes	No parameter
1,2-Dihaloalkanes with Other Electron-Withdrawing Substituents	No parameter
5-pyrazolone derivatives	No parameter
Alcohols	No parameter
Alkanes	No parameter
Allyl glycidyl and benzyl glycidyl ethers (non reactive)	No parameter

Aminophenol derivatives (non reactive)	No parameter
Amphoteric surfactants	No parameter
Anionic surfactants	No parameter
Cationic surfactants	No parameter
Conjugated alpha,beta-unsaturated aldehydes (non reactive)	No parameter
Conjugated alpha,beta-unsaturated esters (non reactive)	No parameter
Conjugated alpha,beta-unsaturated ketones (non reactive)	No parameter
Coumarin Derivatives	No parameter
Cyclopropenones	No parameter
Ethylenediamine, Polyethylene Amines and N,N-Dialkyl-alpha,omega Alkanediamines	No parameter
Guanidines	No parameter
Heterocyclic substituted urea compound with formaldehyde-releasing activity	No parameter
Hydroxybenzene derivatives and quinones (non reactive)	No parameter
Isothiazolone derivatives	No parameter
Mono-halo arenes	No parameter
N-Acylsulfonamides	No parameter
No protein binding alert	No parameter
Non-alpha,beta-conjugated monoaldehydes (non reactive)	No parameter
Non-Conjugated carboxylic acids and esters (non reactive)	No parameter
Non-conjugated mono- and diketones (non reactive)	No parameter
Nonionic surfactants	No parameter
N-substituted aromatic amides	No parameter
p-Aminoarene sulfonamides	No parameter
Phenylenediamine derivatives (non reactive)	No parameter
Squaric acid derivatives	No parameter
Straight-chain primary haloalkanes	No parameter
Substituted 1,4-phenylenediamines and 4-aminophenyl ethers	No parameter
Substituted nitrosoarenes	No parameter
Sulfanilic Acid Derivatives	No parameter
Thiols and disulfides (non reactive)	No parameter
Vaniline derivatives	No parameter
Vinyl pyridines	No parameter
Grey zone 9-21% (DPRA 13%)	
Alkyl alkanesulfonates and dilakylsulfates	No parameter
Allyl glycidyl and benzyl glycidyl ethers (Grey zone)	No parameter
Aminophenol derivatives (Grey zone)	No parameter
Branched acyl halides	No parameter
Conjugated alpha,beta-unsaturated aldehydes (Grey zone)	No parameter
Conjugated alpha,beta-unsaturated esters (Grey zone)	No parameter
Conjugated alpha,beta-unsaturated ketones (Grey zone)	No parameter
Halonitrobenzenes	No parameter
Non-alpha,beta-conjugated monoaldehydes (Grey zone)	No parameter
Non-Conjugated carboxylic acids and esters (Grey zone)	No parameter
Non-conjugated mono- and diketones (Grey zone)	No parameter
Other quinoid structures (Grey zone)	No parameter
Phenylenediamine derivatives (Grey zone)	No parameter

Thiols and disulfides (Grey zone)	No parameter
Total: 73 categories	
Counter category: Out of mechanistic domain	

Similar to other profilers

The profiler is similar to the ***Protein binding potency Cys (DPRA 13%)*** and ***Protein binding potency*** profilers. All three profilers are focused on possibility of chemicals to interact with proteins on the *in chemico* reactivity level and may provide indication for protein binding potency of chemicals. In this respect ***Protein binding potency Lys (DPRA 13%)*** profiler should be used not as a primary grouping method, but as a secondary method for refining the primary group of chemicals. As a result of this a stringent and more consistent group of chemical responsible for interaction with cell proteins could be obtained.

Short description of update version

SMARTS language for describing molecular patterns, i.e. structural boundaries, structural alerts has been implemented in OECD QSAR Toolbox 4.0. As a result ***Protein binding potency Lys (DPRA 13%)*** has been rewritten. Distinctions are expected in the profiling results between Toolbox v.3.4 and v.4.0 due to:

- Different thresholds used for classification of chemicals – in Toolbox v.3.4 classification of potency categories is as follows: Low reactive (lysine depletion = 5-40%), Moderate reactive (lysine depletion = 40-80%), High reactive (lysine depletion > 80%) while in Toolbox v.4.0 classification of potency categories is as follows: DPRA above 21% (DPRA 13%), DPRA less than 9% (DPRA 13%) and Grey zone 9-21% (DPRA 13%);
- Different number of structural alerts – the profile contains 24 structural alerts in Toolbox v.3.4 and 73 structural alerts in Toolbox v.4.0;
- Different number of chemicals used to extract the structural alerts – 110 chemicals for structural alerts implemented in Toolbox v.3.4 and 228 chemicals used for Toolbox v.4.0;
- Different interpretation of the molecular structures, e.g. for heterocyclic/heteroaromatic compounds.

Disclaimer

The structural boundaries used to define the chemical classes (e.g. “Alcohol” – chemical class from “Organic functional group” profiler) or alerting groups responsible for the binding with biological macromolecules (e.g. “Aldehydes” – structural alert for protein binding), represent structural functionalities in the molecule which could be used for building chemical categories for subsequent data gap filling. They are not recommended to be used directly for prediction purposes (as SARs).