About section of a profiler
Name of the profiler
Protein binding potency Cys (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 77 structural alerts extracted from about 229 chemicals with experimentally measured cysteine depletion values. The set of 77 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 a 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 cysteine 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 cysteine 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 (cysteine) measured as percent peptide depletion. The data has been obtained by measuring the covalent binding of the target chemicals with the thio group of cysteine (Cys).
c) The profiler was based on a dataset of 229 chemicals with experimental Cys depletion values. A list of 77 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%)	
1,2- and 1,3-Diketones (reactive)	No parameter
1,2-Dihaloalkanes with Other Electron-Withdrawing Substituents	No parameter
2,4-Dinitrohaloarenes and 2,4-Dinitrophenyl thiocyanates	No parameter
Abietic acid	No parameter
Activated 1,3,5-triazine derivatives	No parameter
Alkyl alkanesulfonates	No parameter
alpha,beta-Unsaturated compounds with polarized triple bonds	No parameter
Aminophenol derivatives (reactive)	No parameter
Benzisothiazolinone derivatives	No parameter
Benzyl halides	No parameter
Branched acyl halides	No parameter
Conjugated alpha, beta-unsaturated aldehydes	No parameter
Conjugated alpha, beta-unsaturated esters (reactive)	No parameter
Conjugated alpha, beta-unsaturated ketones (reactive)	No parameter
Cyclopropenones	No parameter
Diacylperoxides	No parameter
Dialkylsulfates	No parameter
Disulfides	No parameter
Epoxides	No parameter
Ethylenediamine and polyethylene amines (reactive)	No parameter
Glycidyl ethers (epoxyethers)	No parameter
Halogenated isothiazolones	No parameter
Heterocyclic substituted urea compound with formaldehyde-releasing activity	No parameter
Hydroquinone and catechol derivatives (reactive)	No parameter
Isocyanates and Isothiocyanates	No parameter

Isothiazolinone derivatives	No parameter
m- and o-Phenylenediamine derivatives	No parameter
Maleic anhydride derivatives	No parameter
Non-Conjugated carboxylic acids and esters (reactive)	No parameter
Non-Conjugated monoaldehydes (reactive)	No parameter
N-Substituted aromatic amides (reactive)	No parameter
Oxazolones	No parameter
p-Phenylenediamine derivatives	No parameter
Primary iodoalkanes	No parameter
Saturated dialdehydes	No parameter
Squaric acid	No parameter
Substituted nitrosoarenes	No parameter
Thiols (reactive)	No parameter
Vinyl pyridines	No parameter
Vinylene 1,2-biscarboxylates	No parameter
DPRA less than 9% (DPRA 13%)	
1,1-Dihaloethenes	No parameter
1,2- and 1,3-Diketones (non reactive)	No parameter
5-pyrazolone derivatives	No parameter
Alcohols	No parameter
Alkanes	No parameter
alpha alkyl cinnamaldehydes	No parameter
Aminophenol derivatives (non reactive)	No parameter
Anionic surfactants	No parameter
Cationic surfactants	No parameter
Conjugated alpha, beta-unsaturated esters (non reactive)	No parameter
Conjugated alpha, beta-unsaturated ketones (non reactive)	No parameter
Coumarin derivatives	No parameter
Cyclic acid anhydrides (non reactive)	No parameter
Ethylenediamine and polyethylene amines (non reactive)	No parameter
Hydroquinone and catechol derivatives (non reactive)	No parameter
Mercaptoalcohols	No parameter
Mono-halo arenes	No parameter
No protein binding alert	No parameter
Non-Conjugated carboxylic acids and esters (non reactive)	No parameter
Non-Conjugated monoaldehydes (non reactive)	No parameter
N-Substituted aromatic amides (non reactive)	No parameter
Other alpha, beta-unsaturated compounds with polarized double bonds (non reactive)	No parameter
p-Aminoarene Sulfonamides	No parameter
Sulfanilic acid derivatives	No parameter
Thiols (non reactive)	No parameter
Vaniline derivatives	No parameter
Grey zone 9-21% (DPRA 13%)	
1,3-Diketones	No parameter
alpha, beta-unsaturated acids	No parameter
Conjugated alpha, beta-unsaturated ketones (Grey zone)	No parameter

Cyclic acid anhydrides (Grey zone)	No parameter
Hydroquinone and catechol derivatives (Grey zone)	No parameter
Lactones fused to aromatic rings	No parameter
N,N-Dialkyl-alpha,omega-Alkanediamines	No parameter
Non-Conjugated carboxylic acids and esters (Grey zone)	No parameter
Non-Conjugated monoaldehydes (Grey zone)	No parameter
Polysorbates	No parameter
Primary haloalkanes with short alkyl chain	No parameter
Total: 77 categories	
Counter category: Out of mechanistic domain	
Similar to other profilers	
The profiler is similar to the ***Protein binding potency Lys (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 Cys (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 Cys (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 (cysteine depletion = 5-40%), Moderate reactive (cysteine depletion = 40-80%), High reactive (cysteine 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 32 structural alerts in Toolbox v.3.4 and 77 structural alerts in Toolbox v.4.0; • Different number of chemicals used to extract the structural alerts – 112 chemicals for structural alerts implemented in Toolbox v.3.4 and 229 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).	