About section of a profiler
Name of the profiler
Protein binding alerts for skin sensitization according to GHS
Developer; Donator; date; version
Developer: Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria,   *Donator:*   Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria   *Version:* 1.1   December 2017
Relevance/Applicability to endpoint(s)
The profiler is based on recently developed OASIS TIMES model for predicting skin sensitization according to GHS criteria. The protein binding alerts are extracted from 517 chemicals used as a training set for the model. In the current version of the profiler are available 135 alerts, classifying chemicals into GHS categories 1A and 1B. The borders of Category 1B are slightly modified in the model and respectively in the profiler. As a result the classification thresholds are the following: • Category 1A – EC3 (LLNA) ≤ 2%; NOEL (HRIPT)≤ 500 μg/cm2   • Category 1B – 2%; < EC3 (LLNA) < 50%; 500 μg/cm2 < NOEL (HRIPT) < 12 500 μg/cm2   • No alert found – EC3 (LLNA) ≥ 50%; Negative (LLNA); NOEL (HRIPT) > 12 500 μg/cm2   Each alert is associated with reaction mechanistic domain, e.g. Schiff base formation, Michael addition, Acylation, etc. and it is specified in the help file supporting the mechanism of interaction of the alerting group with skin proteins.   The profiler consists of structural and parametric (log KOW) requirements.
Relevance/Applicability to particular chemical classes
This profiler is applicable to those organic chemicals that have presence of at least one of the 135 protein binding alerts specified within the profiler. The presence of some protein binding alerts is conbined with specific logKow ranges, i.e. the profiler contains structural and parametric boundaries. The absence of a protein binding alert should not be taken as an absence of toxicity.
Approach used to develop the profiler - Concise but informative description of:
a) The aim of this profiler is to investigate the presence of alerts within the target molecules responsible for interaction with proteins and to provide potency classification of the target chemicals.
b) The profiler was developed from a mechanistic rationale that the molecular initiating event for skin sensitisation for low molecular weight chemicals is due to covalent binding of chemicals to proteins in the skin.
c) The training set of 517 chemicals was used to define the boundaries of the protein binding alerts for skin sensitization according to GHS classification. Currently, there are 137 protein binding alerts classifying chemicals into GHS categories 1A and 1B. Distribution of the alerts across GHS categories is as follows: 87 alerting groups belong to Category 1A and 48 alerting groups belong to Category 1B.   This profiler accounts for incapability of some chemicals having an alert to interact with skin due to electronic and steric factors. This is explicitly defined by inhibition masks

associated with some of the alerts.

d) Reference source	

Summary description of profiles/alerts within the profiler

Profile/structural alert	Number of chemicals analysed	Number of chemicals associated with skin sensitisation
Skin sensitization Category 1A		
(Thio)Acyl and (thio)carbamoyl halides, cyanides, azides, etc.	6	2/6
1,2-Dicarbonyls, 1,3-Dicarbonyls	4	3/4
2-(Haloalkylidene)phenylhydrazines	0	0/0
Activated (di)aryl esters	2	2/2
Activated (thio)esters	0	0/0
Activated aryl and heteroaryl compounds	17	16/17
Activated Carbonyl compounds	2	2/2
Activated electrophilic ethenylarenes	0	0/0
Active cyclic agents	1	1/1
Alkene sultones	0	0/0
Allylic primary pseudohalides	0	0/0
Alpha- or beta-halo ethers	0	0/0
alpha, beta-Aldehydes	3	2/3
alpha, beta-carbonyl compounds with polarized double bond	23	19/23
alpha,beta-Carbonyl compounds with polarized triple bond	0	0/0
alpha-Activated benzyls	5	5/5
alpha-Activated haloalkanes	1	1/1
alpha-Ketoesters	0	0/0
Anhydrides (sulphur analogues of anhydrides)	4	4/4
Arene sulfinic acids	0	0/0
Aromatic carbonyl compounds	3	2/3
Aryliodonium salts	0	0/0
Azlactones and unsaturated lactone derivatives	4	4/4
Azocarbonamides	0	0/0
Azomethyne type compounds	0	0/0
Azomethynes with a sulfo leaving group	0	0/0
Azoxy compounds	0	0/0
Benzoyl phosphine oxides	0	0/0
beta-Lactams	1	1/1
Bifunctional alpha, beta-carbonyl containing compounds	1	1/1
Bis Aldehydes	5	4/5
Bis Epoxides	4	4/4
Carbodiimides	0	0/0
Conjugated systems with electron	0	0/0

withdrawing groups		
Cyclopropenones	1	1/1
Diacyl peroxides, anhydrides (sulphur analogues of diacyl peroxides)	1	1/1
Diol epoxides	2	2/2
Dithiocarbamate salts	2	2/2
Dithiocarbamates	1	1/1
Dithioesters	0	0/0
Epoxides, Aziridines and Sulfuranes	2	2/2
Formaldehyde	4	4/4
Generated free radicals	10	9/10
Guanidines		
Halogenated five membered aromatic compounds	0	0/0
Halogenated isothiazolones	2	2/2
Halogenated nitroquinones	0	0/0
Heteroarene sulfenamides	0	0/0
Iodoalkynes	1	1/1
Isocyanates, Isothiocyanates	6	6/6
Isothiazolidin-3-ones (sulphur) and Benzoisothiazolinone	2	2/2
Isothiazolone derivatives	4	4/4
Ketenes	0	0/0
Lactones	2	2/2
Mercury compounds	0	0/0
Mustard compounds	0	0/0
N-Chloro-sulphonamides	1	1/1
N-Haloacylamides	0	0/0
Nitroalkenes	0	0/0
Nitrosoalkenes	4	3/4
N-nitroso compounds	9	9/9
N-nitroso_compounds	9	9/9
N-oxicarbonyl amides, N-Acyloxy-N-alkoxyamides	0	0/0
N-Sulfonylazomethynes	1	1/1
Organic sulfonyl azides	0	0/0
Organic thiosulfates	0	0/0
Phenyl carbonates	0	0/0
Phosphonyl halides or cyanide	0	0/0
Phosphoranylidene compounds	0	0/0
Polarised alkene - alkenyl pyridines, pyrazines, pyrimidines or triazines	2	2/2
Polarised Alkenes - sulfonates	0	0/0
Polarised Alkenes- sulfinyl	0	0/0
Polarised Alkenes- sulfones	1	1/1
Polarised alkynes, alkinyl pyridines, pyrazines, pyrimidines, triazines	0	0/0

Quinone(s)/imines, Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones, Naphtoquinone(s)/imines	91	56/91
Substituted benzyl benzoates	0	0/0
Sulfates	1	1/1
Sulfenyl halides	0	0/0
Sulfonates	4	3/4
Sulphonyl halides or cyanides	0	0/0
Sultones	0	0/0
Thiocyanates	2	2/2
Thio-lactones	0	0/0
Thiosulfinates	0	0/0
Thiosulfonates	0	0/0
Thiourea compounds	0	0/0
Vinyl-type compounds with electron-withdrawing groups	2	2/2
Skin sensitization Category 1B		
(Thio)Phosphates	1	1/1
1,2-Dicarbonyls, 1,3-Dicarbonyls_low activity	13	12/13
a,b-Unsaturated oximes	4	1/4
Activated (di)aryl esters_low activity	4	4/4
Activated (thio)esters_low ativity	1	1/1
Activated alkyl esters	7	7/7
Activated aryl and heteroaryl compounds_low activity	17	14/17
Active cyclic agents_low activity	2	2/2
Aldehydes	63	48/63
Alkyl diesters	0	0/0
Alkyl halides	23	22/23
alpha, beta-Aldehydes_low activity	14	12/14
alpha, beta-carbonyl compounds with polarized double bond_low reactivity	36	26/36
alpha,beta-Carbonyl compounds with polarized triple bond_low activity	1	1/1
alpha-activated acetates	8	7/8
alpha-Activated haloalkanes_low activity	2	2/2
alpha-Ketoesters_low activity	1	1/1
Amides	2	1/2
Azlactones and unsaturated lactone derivatives_low activity	4	4/4
Benzyl or phenethyl salicylates	1	0/1
Benzyl phenyl ethers	1	1/1
Bifunctional alpha, beta-carbonyl containing compounds_low activity	2	2/2
Carbamates	2	1/2
Carbenium ion	1	1/1
C-Nitroso compounds	2	0/2

Conjugated systems with electron withdrawing groups_low activity	3	2/3
Cyanoalkenes	1	1/1
Diacyl peroxides, anhydrides (sulphur analogues of diacyl peroxides)_low activity	0	0/0
Dithiocarbamate ester disulfides	2	2/2
Epoxides, Aziridines and Sulfuranes_low activity	20	16/20
Generated free radicals_low active	2	1/2
Hydroperoxides	37	36/37
Ketones	15	14/15
Lactones_low activity	1	1/1
N-Carbonyl heteroaryl amines	0	0/0
N-Carbonylsulfonamides	1	0/1
Nitrosoalkenes_low activity	1	1/1
N-nitroso compounds_low activity	0	0/0
N-nitroso_compounds_low activity	0	0/0
Phosphonates	0	0/0
Pyranones, Pyridones (and related nitrogen chemicals)	0	0/0
Pyrazolones and pyrazolidinones	2	1/2
Quinone(s)/imines, Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones, Naphtoquinone(s)/imines_low activity	9	5/9
Sulfates_low activity	1	1/1
Sulfonates_low activity	1	1/1
Sultones_low activity	0	0/0
Thiols, (poly)sulfides and dithiocarbamate ester disulfides	8	5/8
Total	571	459/571

Counter profiler: No alert found

Similar to other profilers

This profiler is similar to the general mechanistic *Protein binding by OASIS a*nd enpoitnt specific *Protein binding alerts for skin sensitization by OASIS*. However this profiler is endpoint specific and is designed to indicate chemicals could interact with proteins and could cause skin sensitization. As might be expected there is significant overlap between the profilers (given that the MIE is the same); however, the structural alerts in the endpoint specific profiler are focussed on chemistry associated with covalent binding to skin proteins associated with skin allergy. In this respect the specificity of the profiler is codded by using a specific inhibition masks associated with some of structural alerts. As such, this 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 causing skin sensitization effect 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 4.1. As a result *"Protein binding alerts for skin sensitization according to GHS"* has been implemented.

The updates in the profiler available in QSAR Toolbox 4.2 consist of:

- Addition of local training sets to the corresponding structural alerts including the following information:
    - Chemical ID (CAS, Name, SMILES)
    - Representative experimental data - in case of multiple data the worst case scenario or expert judgement is used
    - Metabolic activation
    - Bioassay (LLNA and HRIPT)
    - References

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).