| About section of a profiler |
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| **Name of the profiler** |
| Protein binding by OASIS |
| **Developer; Donator; date; version** |
| ***Developer:***<br>Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria,<br><br>***Donator:***<br>Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria; L'Oréal; ExxonMobil; Procter & Gamble; Unilever; Research Institute for Fragrance Materials (RIFM), Dow Chemical, Danish National Food Institute, Denmark<br><br>***Version*:** 1.5<br>June 2017 |
| **Relevance/Applicability to endpoint(s)** |
| The profiler is based on the rules defined in the OASIS TIMES models for Skin sensitisation (SS). It consists of 112 structural alerts related to interactions with proteins especially skin proteins and proteins such as topoisomerases, cellular protein adducts, etc. It is believed that positive results are result of interactions with proteins. The list of structural alerts has been separated into 11 mechanistic domains. Each of the mechanistic domains has been separated into more than 2 mechanistic alerts. The profiling result outcome assigns a target to the corresponding structural alert, mechanistic alerts and domain. |
| **Relevance/Applicability to particular chemical classes** |
| This profiler is applicable to those organic chemicals that have presence of at least one of the 112 protein binding alerts specified within the profiler. The presence of protein binding alerts is not bounded with parametric ranges; it is based on structural boundaries only. The absence of a structural alert should not be taken as an absence of toxicity. |
| **Approach used to develop the profiler -** Concise but informative description of: |
| a) The overall rational: The aim of this profiler is to investigate the presence of alerts within the target molecules responsible for interaction with proteins. |
| b) The criteria or the method applied for analysing the training set/the pool of chemicals that inform the profiler: 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) Source of the data/knowledge and total number of chemicals included in the analysis: |
| d) Literature references: |
| **Summary description of <u>profiles/alerts</u> within the profiler** |
| Summary list of the profiler categories is provided below. |
| **Profile categories:** |
| Isothiocyanates, Isocyanates |
| Carbodiimides |
| (Thio) Acetates |
| (Thio)Acyl and (thio)carbamoyl halides and cyanides |
| Anhydrides (sulphur analogues of anhydrides) |

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| Azlactones and unsaturated lactone derivatives |
| Carbamates |
| Diacyl peroxides, anhydrides (sulphur analogues of diacyl peroxides) |
| N-Acylloxysuccinimides |
| N-Carbonyl heteroaryl amines |
| N-Carbonylsulfonamides |
| N-Haloacylamides |
| Phosphonyl halides or cyanides |
| Sulphonyl halides or cyanides |
| Thiosulfinates |
| Thiosulfonates |
| Amides |
| Dithiocarbamate salts |
| Dithiocarbamates |
| Dithioesters |
| Activated (di)aryl esters |
| Activated (thio)esters |
| Activated alkyl diesters |
| Benzyl or phenethyl salicylates |
| Phenyl carbonates |
| Substituted benzyl benzoates |
| Ketenes |
| Active cyclic agents |
| beta-Lactams |
| Cyclopropenones |
| Thio-lactones |
| Tetraalkylammonium ions |
| Guanidines |
| alpha,beta-Aldehydes |
| Lactones |
| Azoxy compounds |
| Activated electrophilic ethenylarenes |
| alpha,beta-Carbonyl compounds with polarized double bonds |
| alpha,beta-Carbonyl compounds with polarized triple bond |
| Bifunctional alpha, beta-carbonyl containing compounds |
| Conjugated systems with electron withdrawing groups |
| Cyanoalkenes |
| Nitroalkenes |
| Nitrosoalkenes |
| N-Sulfonylazomethynes |
| Phosphoranylidene compounds |
| alpha,beta-Unsaturated oximes |
| Polarised alkene - alkenyl pyridines, pyrazines, pyrimidines or triazines |
| Polarised Alkenes – sulfinyl |
| Polarised Alkenes – sulfonates |
| Polarised Alkenes – sulfones |
| Polarised alkynes – alkinyl pyridines, pyrazines, pyrimidines, triazines |
| Azocarbonamides |

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| Pyranones, Pyridones (and related nitrogen chemicals) |
| Quinone methide(s)/imines; Quinoide oxime structure; Nitroquinones, Naphthoquinone(s)/imines |
| Alkene sultones |
| Azomethyme type compounds |
| Ketones |
| C-Nitroso compounds |
| Generated free radicals |
| Hydroperoxides |
| Organic peroxy compounds |
| Benzoyl phosphine oxides |
| 1,2-Dicarbonyls and 1,3-Dicarbonyls |
| Di-substituted alpha,beta-unsaturated aldehydes |
| Activated Carbonyl compounds |
| Aldehydes |
| alpha-Ketoesters |
| Aromatic carbonyl compounds |
| Bis aldehydes |
| Pyrazolones and Pyrazolidinones |
| Carbenium ion |
| Mercury compounds |
| Allyl and propargyl sulfate and sulfonate esters |
| Thiols and disulfide compounds |
| Iodoalkynes |
| N-Nitroso compounds (SN2-Nucleophilic substitution at a Nitrogen atom) |
| N-oxicarbonyl amides, N-Acyloxy-N-alkoxyamides |
| (Thio)Phosphates |
| Alkyl halides |
| alpha-Activated acetates |
| alpha-Activated haloalkanes |
| N-Nitroso compounds (SN2-Nucleophilic substitution at sp3 carbon atom) |
| Phosphonates |
| Sulfates |
| Sulfonates |
| N-Nitroso_compounds (Nucleophilic substitution at the central carbon atom of N-nitroso compounds) |
| Organic thiosulfates and thiosulfonates |
| alpha-Activated benzyls |
| Heteroarene sulfenamides |
| Organic sulfonyl azides |
| Epoxides, Aziridines and Sulfuranes |
| Isothiazolone derivatives |
| Mustards compounds |
| Sultones |
| N-Chloro-sulphonamides |
| 2-(Haloalkylidene)phenylhydrazines |
| Activated alkyl esters and thioesters |
| alpha- or beta-Halo ethers |

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| Benzyl phenyl ethers |
| Isothiazolidin-3-ones (sulphur) and Isothiazolone derivatives |
| Sulfenyl halides |
| Thiocyanates |
| Arenesulfinic acids |
| Thiourea compounds |
| Activated aryl and heteroaryl compounds |
| Halogenated five membered aromatic compounds |
| Halogenated nitroquinones |
| Aryliodonium salts |
| Halogenated isothiazolones |
| Azomethynes with a sulfo leaving group |
| Vinyl-type compounds with electron withdrawing groups |
| **Total: 112 categories** |
| **Counter category:** Not categorized |
| **Similar to other profilers** |
| This profiler is general mechanistic and it is similar to the ***Protein binding alerts for skin sensitization by OASIS*** and ***Protein binding by OECD***. As might be expected there is significant overlap between the profilers (given that the MIE is the same); however, the structural alerts in the general 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 coded 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 4.0. As a result ***Protein binding by OASIS*** has been rewritten. Only small distinctions are expected in the profiling results between Toolbox v.3.4 and v 4.0 due to different interpretation of the molecular structures, e.g. for heterocyclic/heteroaromatic compounds.<br><br>Further general modifications are as follows:<br>1. Ketones - slight correction in the structural boundary - N-atom is removed<br>2. α-Haloalkenes (and related cyano, sulfate and sulphonate substituted chemicals) were renamed to Allyl and propargyl sulfate and sulfonate esters<br>3. The mechanistic alert named Electrostatic interaction of tetraalkylamonium ion with protein carboxylates was deleted<br>4. Removing of the rules defined in the OASIS TIMES models for Cromosomal aberration. Removed are as follows: |

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| **1** | Carbamates |
| **2** | alpha,beta-Unsaturated Carbonyls and Related Compounds |
| **3** | Isothiocyanates |
| **4** | Isocyanates and Diisocyanates |

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| **5** | Pyrazolone and Pyrazolidine-3,5-dione Derivatives |
| **6** | alpha,omega-Dihaloalkanes |
| **7** | Ethenyl Pyridines |
| **8** | Pyrimidines and Purines |
| **9** | Bipyridilium Herbicides |
| **10** | alpha,beta-Unsaturated Carboxylic Acids and Esters |
| **11** | Carboxylic Acid Anhydrides |
| **12** | Halogenated Vicinal Hydrocarbons |
| **13** | Heterocyclic Aromatic Amines |
| **14** | Substituted Phenols |
| **15** | Carboxylic Acid Amides |
| **16** | Arenesulfonamides |
| **17** | N-Substituted Aromatic Amines |
| **18** | Arenecarboxylic Acid Esters |
| **19** | Cyanohydrins |
| **20** | Substituted Anilines |
| **21** | Gallic Acid Esters |
| **22** | Benzoquinoline and Acridine derivatives |
| **23** | N-Alkyl-N-nitrosocarbamates |
| **24** | N-Nitrosoamine Derivatives |
| **25** | Alkylated nitrosoureas and nitrosoguanidines |
| **26** | Dialkyl Alkylphosphonates |
| **27** | Hexahydrotriazine Derivatives |
| **28** | Sterically Hindered Piperidine Derivatives |
| **29** | Hydroxylated Phenols |
| **30** | Propargyl Alcohol Derivatives |
| **31** | Quinoneimine |

Modifications in OECD QSAR Toolbox 4.1 are as follows:

1. The structural boundaries of the category named "Activated aryl esters" were separated into 5 new categories:
   - Activated (di)aryl esters
   - Activated (thio)esters

- Benzyl or phenethyl salicylates
- Phenyl carbonates
- Substituted benzyl benzoates

2. New categories were defined:
   - Bis aldehydes
   - Bifunctional alpha, beta - carbonyl containing compounds
   - Benzyl phenyl ethers
   - Iodoalkynes
   - Alpha - activated acetates
3. The category named "Vinyl type compounds with electron withdrawing groups" were split into 2 categories:
   - Vinyl type compounds with electron withdrawing groups
   - Azomethynes with a sulfo leaving group
4. The category Activated alkyl esters was renamed to Activated alkyl diesters
5. The category Organic thiosulfates was renamed to Organic thiosulfates and thiosulfonates due to addition of a new structural boundary
6. The category Pyranones, Pyridones (and related nitrogen chemicals) were added to the mechanistic alert named "Michael addition on quinoid type compounds"
7. Modifications were also done in the structural boundaries of the following categories based on expert judgement and available training set representatives:
   - Activated aryl and heteroaryl compounds
   - Lactones
   - Aldehydes
   - alpha - ketoesters
   - alpha,beta-Carbonyl compounds with polarized double bonds
   - Dithiocarbamates
   - alpha-Activated benzyls
   - alpha,beta-Aldehydes
   - Conjugated systems with electron withdrawing groups
   - Cyanoalkenes
   - Aromatic carbonyl compounds
   - Activated alkyl esters and thioesters
   - 1,2-Dicarbonyls and 1,3-Dicarbonyls
8. Restore of the mechanistic alert named Electrostatic interaction of tetraalkylamonium ion with protein carboxylates

**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).