About section of a profiler

Name of the profiler

Protein binding alerts for Chromosomal aberration by OASIS

Developer; Donator; date; version

Developer:
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Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria

Version: 1.4
December 2017

Relevance/Applicability to endpoint(s)

The profiler is based on 33 structural alerts accounting for interactions of chemicals with specific proteins, such as topoisomerases, cellular protein adducts, etc. The scope of this profiler is to investigate the ability of target molecules to elicit clastogenicity and/or aneugenicity. Functionalities which bring about steric (or electronic) hindrance in molecules and thus impede interactions with proteins are explicitly defined and associated with some of the alerts as "inhibition" masks.
This profiler is endpoint specific and is designed to indicate chemicals that could interact with topoisomerases, cellular protein adducts. The structural alerts in the endpoint specific profiler are focussed on chemistry associated with covalent binding to proteins associated with Chromosomal aberrations. 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, more consistent group of chemical responsible for causing chromosomal aberration could be obtained.

Relevance/Applicability to particular chemical classes

This profiler is applicable to those organic chemicals that have presence of at least one of the 33 protein binding alerts specified within the profiler. The presence of protein binding alerts is not bounded with parametric ranges; it is rather based on structural boundaries only. Chemicals not classified by the profiler are marked with "No alert found"

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 such as topoisomerases, cellular protein adducts, etc.

b) The profiler consists of 33 structural alerts. The alerts are separated into 9 mechanstic domains. Some of the structural alerts belong to more than one mechanistic domain.

c) The profiler was developed from a dataset of 1082 chemicals that have experimental data for chromosomal aberration.

Summary description of profiles/alerts within the profiler

Profiler alerts	Number of analysed chemicals	Number of chemicals associated with Chromosomal aberration (Correctly predicted chemicals)	Number of Correctly predicted positive chemicals	Number of Correctly predicted negative chemicals
Isocyanates and Diisocyanates	10	8/10	5/8	3/8

Isothiocyanates	4	4/4	4/4	-
Carboxylic Acid Amides	21	20/21	7/20	13/20
Arenecarboxylic Acid Esters	25	25/25	6/25	19/25
Arenesulphonamides	21	19/22	9/19	10/19
Carbamates	22	18/22	10/18	8/18
Carboxylic acid Anhydrides	13	13/13	3/13	10/13
Hexahydrotriazine Derivatives	2	2/2	2/2	-
alpha, beta - Unsaturated Carbonyls and Related Compounds	51	42/51	13/42	29/42
Pyrazolone and Pyrazolidine Derivatives	5	4/5	4/4	0/4
alpha, beta - Unsaturated Carboxylic Acids and Esters	37	29/37	21/29	8/29
Gallic Acid Esters	3	3/3	3/3	-
Hydroxylated phenols	13	11/13	10/11	1/11
N-Subsituted Aromatic Amines	35	28/35	15/28	13/28
Quinoneimines	2	2/2	2/2	-
Substituted Anilines	79	56/79	25/56	31/56
Substituted Phenols	62	58/62	33/58	25/58
Pyrimidines and Purines	18	15/18	12/15	3/15
Ethenyl Pyridines	1	1/1	1/1	-
Propargyl Alcohol Derivatives	2	2/2	2/2	-
Bipyridilium herbicides	2	2/2	2/2	-
Heterocyclic Aromatic Amines	13	12/13	12/13	0/13
Benzoquinolines and Acridines	10	10/10	7/10	3/10
Sterically Hindered Piperidine Derivatives	5	4/5	4/4	-
N-Alkyl-N-nitrosocarbamates	15	15/15	15/15	-
Alkylated nitrosoureas and nitrosoguanidines	18	18/18	18/18	-
N-Nitrosoamine Derivatives	21	20/21	7/20	13/20
Alpha-Activated Haloalkanes	13	8/13	6/8	2/8
Cyanohydrines	2	2/2	1/2	1/2
Nitrogen Mustard	6	6/6	6/6	-
alpha, omega-	2	2/2	2/2	-

Dihaloalkanes				
Halogenated Vicinal Hydrocarbons	21	20/21	11/20	9/20
Dialkyl Alkylphosphonates	5	5/5	5/5	-
Total: 33 Alerts	561	486/561	283/486	203/486
Counter category: No alert found				
Similar to other profilers				
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 alerts for Chromosomal aberrations 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 heteroatomic compounds.
Further general modifications are as follows:
1. Carboxylic Acid Amides – a mask is added prohibiting aryl-azo-keto fragment
2. Substituted Anilines – a mask is added prohibiting aryl-azo-keto fragment
3. Substituted Phenols – masks are added to the queries
4. Hydroxylated Phenols – masks are added to the queries
5. N-Substituted Aromatic Amines - a mask is added
6. alpha,beta-Unsaturated Carbonyls and Related Compounds – a mask is added; the query for alpha,beta-Unsaturated aldehydes is modified
7. Halogenated Vicinal Hydrocarbons – the query is modified by addition of masks, enumeration and explicit H-atoms
8. Heterocyclic aromatic amines - new query is added for triazines

Modifications implemented in OECD QSAR Toolbox 4.1 are as follows:
1. Halogenated vicinal Hydrocarbons
   The general structural definition is extended by addition of the following substituents: hydrogen, hydroxyl group, sulfur, phosphorous and carbon. The addition was necessary due to expert opinion based on newly added chemicals to the training data set.
2. Heterocyclic aromatic amines
   As a result of expansion of the training set with in house tested chemicals new structural mask – trisubstituted triazine with alkyl or arylamino groups is adeded by expert judgment.
3. Substituted phenols
   The structural definition is extended by addition of new mask - alkyl and alkoxy substituted phenols. The need of this mask was expertly specified.
4. alpha,beta-Unsaturated Carbonyls and Related Compounds
   The query for alpha, beta - Unsaturated ketones was expertly modified according to available training set representatives.

The updates in the profiler are: attached local training sets to the structural alerts available in Toolbox 4.2 consist of:
1. Addition of local training sets to the corresponding structural alerts including the following information:
2. Chemical ID (CAS, Name, SMILES)
3. Representative experimental data - in case of multiple data the worst case scenario or expert judgement is used
4. Metabolic activation (without S9 activation)

5. Bioassay (Bacterial Reverse Mutation Assay)
6. 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).