About section of a profiler

Name of the profiler

DNA alerts for CA and MNT by OASIS

Developer; Donator; date; version

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

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

Version: 1.2
December 2017

Relevance/Applicability to endpoint(s)

The profiler was based on DNA reactivity of the Chromosomal aberrations TIMES model. It was based on the 85 structural alerts responsible for interaction of chemicals with DNA. The list of 85 structural alerts has been separated into eight mechanistic domains. The scope of this profiler is to investigate the presence of alerts within the target molecules responsible for interaction with DNA. This profiler accounts for incapability of some chemicals having an alert to interact with DNA due to electronic and steric factors. This is explicitly defined by specific structural requirements associated with the alerts. The profiling result 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 85 DNA binding alerts specified within the profiler.

Approach used to develop the profiler - Concise but informative description of:

a) The overall rationale: The aim of the profiler is to investigate presence of alerts within target molecules responsible for interaction with DNA especially related to chromosomal aberrations and Micronucleus formations.

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 gene mutation of low molecular weight chemicals is due to covalent binding of chemicals to DNA.

c) Source of the data/knowledge and total number of chemicals included in the analysis: The profiler was based on the 85 structural alerts responsible for interaction with DNA analysed in Chromosomal aberrations model. The list of 85 structural alerts has been separated into eight mechanistic domains. This profiler accounts for incapability of some chemicals having an alert to interact with DNA due to electronic and steric factors. This is explicitly defined by specific structural requirements associated with the alerts.

d) Literature references:

1. Mekenyan, O., Dimitrov, S., Serafimova, R., Thompson, E., Kotov, S., Dimitrova, N., and Walker, J. (2004) Identification of the structural requirements for mutagenicity by incorporating molecular flexibility and metabolic activation of chemicals I: TA100. Chem. Res. Toxicol. 17, 753-766.

2. Serafimova, R., Todorov, M., Pavlov, T., Kotov, S., Jacob, E., Aptula, A., and Mekenyan, O. (2007) Identification of the structural requirementsfor mutagencitiy, by incorporating molecular flexibility and metabolic activation of chemicals. II. General Ames mutagenicity model. Chem. Res. Toxicol. 20, 662-676.

Summary description of profiles/alerts within the profiler

Profiler alerts	Number of analysed chemicals	Number of Correctly predicted chemicals	Number of Correctly predicted positive chemicals	Number of Correctly predicted negative chemicals
Nitro Azoarenes and p-Substituted Azobenzenes	3	1/3	0/1	1/1

Nitrobiphenyls and Bridged Nitrobiphenyls	0	0	0	0
Conjugated Nitroalkenes and Five-Membered Aromatic Nitroheterocyclics	5	4/5	4/4	0/4
Nitroaniline Derivatives	15	12/15	6/12	6/12
Fused-Ring Nitroaromatics	7	4/7	4/4	0/4
Nitroarenes with Other Active Groups	7	4/7	2/4	2/4
Nitroalkanes	1	0/1	0/0	0/0
Nitrophenols, Nitrophenyl Ethers and Nitrobenzoic Acids	12	4/12	2/4	2/4
p-Substituted Mononitrobenzenes	2	1/2	1/1	0/1
Polynitroarenes	9	7/9	2/7	5/7
N-Aryl-N-Acetoxy(Benzoyloxy) Acetamides	1	1/1	1/1	0/1
Amino Anthraquinones	5	5/5	3/5	2/5
Fused-Ring Primary Aromatic Amines	17	14/17	7/14	7/14
p-Aminobiphenyl Analogs	1	1/1	1/1	0/1
Single-Ring Substituted Primary Aromatic Amines	47	38/47	25/38	13/38
Hydrazine Derivatives	7	5/7	4/5	1/5
Specific Acetate Esters	17	15/17	4/15	11/15
Alpha,Beta-Unsaturated Aldehydes	10	9/10	3/9	6/9
Alkylphosphates, Alkylthiophosphates and Alkylphosphonates	31	21/31	10/21	11/21
Diazenes and Azoxyalkanes	2	2/2	2/2	0/2
Arenediazonium Salts	0	0	0	0
Organic Peroxy Compounds	3	3/3	0/3	3/3
Sulfonyl Halides	0	0	0	0
Thiols	3	2/3	1/2	1/2
N-acetoxyamines	1	1/1	1/1	0/1
Alkylnitrites	0	0	0	0
Diazoalkanes	0	0	0	0
Quinoneimines	7	6/7	2/6	4/6
Polarized Haloalkene Derivatives	3	3/3	3/3	0/3
Haloisothiazolinones	0	0	0	0
Haloalkane Derivatives with Labile Halogen	4	4/4	4/4	0/4

Sultones	1	1/1	1/1	0/1
Vicinal Dihaloalkanes	26	20/26	9/20	11/20
Acyl Halides	2	2/2	1/2	1/2
Monohaloalkanes	3	1/3	1/1	0/1
Haloalkanes Containing Heteroatom	17	9/17	5/9	4/9
Haloalkenes with Electron-Withdrawing Groups	8	6/8	1/6	5/6
Geminal Polyhaloalkane Derivatives	27	23/27	8/23	15/23
Alpha-Haloethers	0	0	0	0
Specific Imine and Thione Derivatives	8	7/8	3/7	4/7
Dicarbonyl compounds	10	6/10	6/6	0/6
Quinoline Derivatives	9	6/9	0/6	6/6
Sulfonyl Azides	0	0	0	0
Pyrrolizidine Derivatives	2	2/2	0/2	2/2
Aminoacridine DNA Intercalators	2	2/2	2/2	0/2
Epoxides and Aziridines	19	16/19	15/16	1/16
Quinones and Trihydroxybenzenes	21	10/21	6/10	4/10
Four- and Five-Membered Lactones	4	2/4	1/2	1/2
C-Nitroso Compounds	0	0	0	0
N-Nitroso Compounds	56	50/56	35/50	15/50
Sulfonates and Sulfates	6	6/6	6/6	0/6
N-Acyloxy(Alkoxy) Arenamides	0	0	0	0
Haloalcohols	4	4/4	4/4	0/4
Acyclic Triazenes	0	0	0	0
Nitrogen and Sulfur Mustards	5	2/5	2/2	0/2
Polycyclic Aromatic Hydrocarbon and Naphthalenediimide Derivatives	11	8/11	3/8	5/8
Coumarins	3	3/3	2/3	1/3
N-Hydroxylamines	5	5/5	5/5	0/5
DNA Intercalators with Carboxamide and Aminoalkylamine Side Chain	19	14/19	1/14	13/14
Halofuranones	1	1/1	1/1	0/1
Anthrones	0	0	0	0
Triarylimidazole and Structurally Related DNA Intercalators	0	0	0	0
Hydroxamic Acids	2	2/2	2/2	0/2
Haloalkene Cysteine S-Conjugates	0	0	0	0
Acridone, Thioxanthone,	1	1/1	1/1	0/1

Xanthone and Phenazine Derivatives				
Flavonoids	2	2/2	1/2	1/2
N,N-Dialkyldithiocarbamate derivatives	2	0/2	0/0	0/0
Quinone methides	0	0	0	0
Alpha-Beta Conjugated Alkene Derivatives with Geminal Electron-Withdrawing Groups	1	0/1	0/0	0/0
N-Hydroxyethyl Lactams	0	0	0	0
Quinolone Derivatives	1	1/1	0/1	1/1
Non-Cyclic Alkyl Phosphoramides and Thionophosphoramides	1	0/1	0/0	0/0
Organic Diselenides and Ditellurides	0	0	0	0
Peroxyacyl Nitrates	0	0	0	0
Quinoxaline-Type 1,4-Dioxides	0	0	0	0
Organic Azides	1	1/1	1/1	0/1
Specific 5-Substituted Uracil Derivatives	0	0	0	0
Bleomycin and Structurally Related Chemicals	1	1/1	1/1	0/1
Short-Chain Alkyltin and Alkylgermanium Halides	0	0	0	0
Perfluoroalkyl Hypohalites	0	0	0	0
Propyne Derivatives	0	0	0	0
Haloepoxides and Halooxetanes	0	0	0	0
1,2,5-Thiadiazole 1,1-dioxide derivatives	0	0	0	0
N-Trihalomethyldiacylimides	0	0	0	0
N-methylol derivatives	0	0	0	0
No alert found				
Total: 85 alerts	501	381/501	216/381	165/381
Counter category: No alert found				
Similar to other profilers				
This profiler is similar to the general mechanistic profilers ***DNA binding by OASIS*** and ***DNA binding by OECD*** and endpoint specific profiler ***DNA alerts for AMES by OASIS.***				
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 ***DNA for CA and MNT 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. Further general modifications are as follows:				

1. Quinoxaline-Type 1,4-Dioxides - modified– a mask forbidding fused aromatics is added
2. Four- and Five-Membered Lactones - modified- prohibition (expressed with NOT) for anhydrides
3. Quinone Methides – modified– presence of H-atom at beta position towards carbonyl atom
4. Conjugated Nitroalkenes and Five-Membered Aromatic Nitroheterocyclics – new name – two alerts are united in one alert – former Conjugated Nitro Compounds and Five-Membered Aromatic Nitroheterocycles
5. Haloalcohols – modified- in query #2, I-atom is removed - equally to general mechanistic profiler
6. Haloalkanes Containing Heteroatom – modified- explicit H-atoms are added
7. Haloalkenes with Electron-Withdrawing Groups - prohibition (expressed with NOT) for S-(2-chlorovinyl)-L-cysteine fragment
8. Sulfonates and Sulfates – modified - enumeration is added with O-, N and C{ar} atoms
9. Single-Ring Substituted Primary Aromatic Amines – modified – atomic qualifier forbidding fused aromatics is added
10. Nitro Azoarenes and p-Substituted Azobenzenes – new name - the category has a new name and new query for p-Substituted Azobenzenes is added
11. Alkylnitrites – modified - modified- prohibition (expressed with NOT) for nitro group and introduction of enumeration containing H-atom and C{sp3} atom
12. N-methylol derivatives – new category is added
13. Fused-Ring Primary Aromatic Amines - modified- a mask is added
14. Perfluoroalkyl Hypohalites - a new category is added
15. Propyne Derivatives- a new category is added
16. Haloepoxides and Halooxetanes- a new category is added

The updates in QSAR Toolbox 4.2 are attaching of local training sets to the structural alerts as follows:

- Addition of local training sets to the corresponding structural alerts including:
  - Chemical ID (CAS, Name, SMILES)
  - Representative experimental data - in case of multiple data the worst case scenario or expert judgement is used
  - Metabolic activation (without S9 activation)
  - Bioassay (Bacterial Reverse Mutation Assay)
  - 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).