About section of a profiler
Name of the profiler
DNA binding by OASIS
Developer; Donator; date; version
Developer: Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria, ***Donator:*** Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria ***Version:*** 1.5 December 2017
Relevance/Applicability to endpoint(s)
DNA binding by OASIS is a general mechanistic profiler, consisting of list of structural alerts. The profiler relies on the alerts from the AMES Ames mutagenicity TIMES model. The profiler is based on 85 structural alerts responsible for interaction of chemicals with DNA. The scope of the profiler is to investigate presence of alerts within target molecules which may interact with DNA. The list of 85 structural alerts has been separated into eight mechanistic domains. 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. The presence of DNA binding alerts 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 overall rationale: The aim of the profiler is to investigate presence of alerts within target molecules which may be responsible for interaction with DNA.
b) The criteria or the method applied for analysing the training set/the pool of chemicals that inform the profiler: The trainng set chemicals have been analysed based on identification for presence or absence of DNA binding alert.
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 analyzed in Ames Mutagenicity model. The list of 85 structural alerts has been separated into eight mechanistic domains.
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

Profile/structural alert	Number of analysed chemicals	Number of chemicals associated with Ames mutagenicity
Nitro Azoarenes and p-Substituted Azobenzenes	74	46/74

Nitrobiphenyls and Bridged Nitrobiphenyls	38	28/38
Conjugated Nitroalkenes and Five-Membered Aromatic Nitroheterocyclics	36	36/36
Nitroaniline Derivatives	48	40/48
Fused-Ring Nitroaromatics	46	42/46
Nitroarenes with Other Active Groups	40	26/40
Nitroalkanes	5	4/5
Nitrophenols, Nitrophenyl Ethers and Nitrobenzoic Acids	45	24/45
p-Substituted Mononitrobenzenes	13	11/13
Polynitroarenes	30	24/30
N-Aryl-N-Acetoxy(Benzoyloxy) Acetamides	6	5/6
Amino Anthraquinones	27	10/27
Fused-Ring Primary Aromatic Amines	73	25/73
p-Aminobiphenyl Analogs	32	15/32
Single-Ring Substituted Primary Aromatic Amines	63	13/63
Hydrazine Derivatives	54	38/54
Alpha,Beta-Unsaturated Aldehydes	31	10/31
Specific Acetate Esters	68	13/68
Alkylphosphates, Alkylthiophosphates and Alkylphosphonate	46	13/46
Diazenes and Azoxyalkanes	3	2/3
Arenediazonium Salts	2	2/2
Organic Peroxy Compounds	44	28/44
Sulfonyl Halides	8	4/8
Thiols	34	7/34
N-Acetoxyamines	26	25/26
Alkylnitrites	8	7/8
Diazoalkanes	8	8/8
Quinoneimines	11	4/11
Polarized Haloalkene Derivatives	13	10/13
Haloisothiazolinones	1	1/1
Haloalkane Derivatives with Labile Halogen	37	28/37
Sultones	1	1/1
Vicinal Dihaloalkanes	41	15/41
Acyl Halides	26	6/26
Monohaloalkanes	8	7/8

Haloalkanes Containing Heteroatom	76	58/76
Haloalkenes with Electron-Withdrawing Groups	15	9/15
Geminal Polyhaloalkane Derivatives	100	45/100
Alpha-Haloethers	8	6/8
Specific Imine and Thione Derivatives	24	9/24
Dicarbonyl Compounds	13	10/13
Quinoline Derivatives	51	13/51
Sulfonyl Azides	1	1/1
Pyrrolizidine Derivatives	5	2/5
Aminoacridine DNA Intercalators	29	27/29
Epoxides and Aziridines	75	52/75
Quinones and Trihydroxybenzenes	122	54/122
Four- and Five-Membered Lactones	28	8/28
C-Nitroso Compounds	12	8/12
N-Nitroso Compounds	48	29/48
Sulfonates and Sulfates	33	28/33
N-Acyloxy(Alkoxy) Arenamides	30	30/30
Haloalcohols	15	13/15
Acyclic Triazenes	19	12/19
Nitrogen and Sulfur Mustards	47	44/47
Polycyclic Aromatic Hydrocarbon and Naphthalenediimide Derivatives	47	15/47
Coumarins	30	8/30
N-Hydroxylamines	65	37/65
DNA Intercalators with Carboxamide and Aminoalkylamine Side Chain	118	39/118
Halofuranones	19	19/19
Anthrones	6	4/6
Triarylimidazole and Structurally Related DNA Intercalators	9	8/9
Hydroxamic Acids	6	5/6
Haloalkene Cysteine S-Conjugates	7	7/7
Acridone, Thioxanthone, Xanthone and Phenazine Derivatives	27	24/27
Flavonoids	6	3/6
N,N-Dialkyldithiocarbamate	8	7/8

Derivatives		
Quinone Methides	3	0/3
Alpha-Beta Conjugated Alkene Derivatives with Geminal Electron-Withdrawing Groups	14	1/14
N-Hydroxyethyl Lactams	1	1/1
Quinolone Derivatives	5	4/5
Non-Cyclic Alkyl Phosphoramides and Thionophosphoramides	1	0/1
Organic Diselenides and Ditellurides	1	1/1
Peroxyacyl Nitrates	1	1/1
Quinoxaline-Type 1,4-Dioxides	2	2/2
Organic Azides	1	1/1
Specific 5-Substituted Uracil Derivatives	1	1/1
Bleomycin and Structurally Related Chemicals	2	2/2
Short-Chain Alkyltin and Alkylgermanium Halides	1	1/1
Perfluoroalkyl Hypohalites	1	1/1
Propyne Derivatives	1	1/1
Haloepoxides and Halooxetanes	3	3/3
1,2,5-Thiadiazole 1,1-dioxide derivatives	0	0
N-Trihalomethyldiacylimides	0	0
N-methylol derivatives	0	0
No alert found		
Total: 85 alerts	2183	1232

Similar to other profilers

This profiler is similar to the general mechanistic profiler ***"DNA binding by OECD"*** and endpoint specific profiler ***"DNA alerts for AMES by OASIS"*** and ***"DNA alerts for CA and MN by OASIS"***. Also it is similar to the ***"In vitro mutagenicity (Ames test) alerts by ISS"*** profiler to a certain extent. However, this profiler is general mechanistic and includes structural boundaries which are defined based on chemicals functionalities which may interact with DNA from theoretical point of view. These rules could be considered as necessary conditions for eliciting positive Ames effects and they are not supported by experimental data. Hence, general mechanistic profilers could not be considered as alerts for Ames mutagenicity. For example, Single-Ring Substituted Primary Aromatic Amines in the "DNA binding by OASIS" profiler includes only aniline moiety to describe potential reactivity towards DNA. However, for increasing probability of chemicals to cause positive Ames mutagenicity effect, additional structural requirements not included in this profile need to be defined. Because of that general mechanistic DNA binding profilers are considered as suitable for formation of chemical categories for read across rather than use them as SARs.

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 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.
Further general modifications are as follows:
1. Quinone Methides - modified - presence of H-atom at beta position towards carbonyl atom
2. Alkylnitrites - modified - prohibition (expressed with NOT) for nitro group and introduction of enumeration containing H-atom and C{sp3} atom
3. 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
4. Nitro Azoarenes and p-Substituted Azobenzenes – the category has a new name and new query for p-Substituted Azobenzenes is added
5. Quinoxaline-Type 1,4-Dioxides - modified – a mask forbidding fused aromatics is added

The modification for QSAR Toolbox v.4.2 is:
1. The mechanistic justification for the category Sulfonul halides is replaced with the correct one.
2. The category Haloalkane Derivatives with Labile Halogen is slightly modified in order a cyclic double bond to meet the criteria too.

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).