About section of a profiler

Name of the profiler

DNA alerts for AMES 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)

The profiler was based on the Ames mutagenicity 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 Ames mutagenicity.

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 for 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 analyzed in Ames Mutagenicity model. The list of 85 structural alerts has been separated into weight 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 requirements for mutagenicity, 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	74	59/74	38/59	21/59

Azobenzenes				
Nitrobiphenyls and Bridged Nitrobiphenyls	38	30/38	25/30	5/30
Conjugated Nitroalkenes and Five-Membered Aromatic Nitroheterocyclics	36	36/36	36/36	0/36
Nitroaniline Derivatives	48	43/48	38/44	5/44
Fused-Ring Nitroaromatics	46	44/46	42/44	2/44
Nitroarenes with Other Active Groups	40	33/40	19/33	14/33
Nitroalkanes	5	4/5	4/4	0/4
Nitrophenols, Nitrophenyl Ethers and Nitrobenzoic Acids	45	37/45	16/37	21/37
p-Substituted Mononitrobenzenes	13	11/13	11/11	0/11
Polynitroarenes	30	25/30	20/25	5/25
N-Aryl-N-Acetoxy(Benzoyloxy) Acetamides	6	5/6	5/5	0/5
Amino Anthraquinones	27	22/27	10/22	12/22
Fused-Ring Primary Aromatic Amines	73	58/73	20/58	38/58
p-Aminobiphenyl Analogs	32	25/32	12/25	13/25
Single-Ring Substituted Primary Aromatic Amines	63	37/63	10/37	27/37
Hydrazine Derivatives	54	39/54	27/39	12/39
Alpha,Beta-Unsaturated Aldehydes	31	28/31	7/28	21/28
Specific Acetate Esters	68	55/68	7/55	48/55
Alkylphosphates, Alkylthiophosphates and Alkylphosphonates	46	40/46	12/40	28/40
Diazenes and Azoxyalkanes	3	2/3	2/2	0/2
Arenediazonium Salts	2	2/2	2/2	0/2
Organic Peroxy Compounds	44	40/44	27/40	13/40
Sulfonyl Halides	8	7/8	3/7	4/7
Thiols	34	31/34	6/31	25/31
N-acetoxyamines	26	25/26	25/25	0/25
Alkylnitrites	8	7/8	7/7	0/7
Diazoalkanes	8	8/8	8/8	0/8

Quinoneimines	11	9/11	4/9	5/9
Polarized Haloalkene Derivatives	13	10/13	10/10	0/10
Haloisothiazolinones	1	1/1	1/1	0/1
Haloalkane Derivatives with Labile Halogen	29	25/29	20/25	5/25
Sultones	1	1/1	1/1	0/1
Vicinal Dihaloalkanes	41	29/41	8/29	21/29
Acyl Halides	26	22/26	5/22	17/22
Monohaloalkanes	8	7/8	7/7	0/7
Haloalkanes Containing Heteroatom	76	63/76	45/63	18/63
Haloalkenes with Electron-Withdrawing Groups	15	11/15	6/11	5/11
Geminal Polyhaloalkane Derivatives	100	83/100	32/83	51/83
Alpha-Haloethers	8	5/8	5/5	0/5
Specific Imine and Thione Derivatives	24	16/24	6/16	10/16
Dicarbonyl compounds	13	10/13	10/10	0/10
Quinoline Derivatives	51	40/51	8/40	32/40
Sulfonyl Azides	1	1/1	1/1	0/1
Pyrrolizidine Derivatives	5	5/5	2/5	3/5
Aminoacridine DNA Intercalators	29	26/29	26/26	0/26
Epoxides and Aziridines	75	68/75	47/67	21/67
Quinones and Trihydroxybenzenes	122	98/122	41/98	57/98
Four- and Five-Membered Lactones	28	23/28	7/23	16/23
C-Nitroso Compounds	12	11/12	8/11	3/11
N-Nitroso Compounds	48	44/48	27/44	17/44
Sulfonates and Sulfates	33	29/33	25/29	4/29
N-Acyloxy(Alkoxy) Arenamides	30	30/30	30/30	0/30
Haloalcohols	15	13/15	13/13	0/13
Acyclic Triazenes	19	17/19	12/17	5/17
Nitrogen and Sulphur Mustards	47	40/47	37/40	3/40
Polycyclic Aromatic Hydrocarbon and Naphthalenediimide Derivatives	47	40/47	11/40	29//40
Coumarins	30	29/30	7/29	22/29
N-Hydroxylamines	65	52/65	33/52	19/52

DNA Intercalators with Carboxamide and Aminoalkylamine Side Chain	118	101/118	22/101	79/101
Halofuranones	19	17/19	17/17	0/17
Anthrones	6	4/6	3/4	1/4
Triarylimidazole and Structurally Related DNA Intercalators	9	8/9	8/8	0/8
Hydroxamic Acids	6	5/6	5/5	0/5
Haloalkene Cysteine S-Conjugates	7	6/7	6/6	0/6
Acridone, Thioxanthone, Xanthone and Phenazine Derivatives	27	26/27	23/26	3/26
Flavonoids	6	6/6	3/6	3/6
N,N-Dialkyldithiocarbamate derivatives	8	7/8	7/7	0/7
Quinone methides	3	0/3	0/3	0/3
Alpha-Beta Conjugated Alkene Derivatives with Geminal Electron-Withdrawing Groups	14	13/14	0/13	13/13
N-Hydroxyethyl Lactams	1	1/1	1/1	0/1
Quinolone Derivatives	5	5/5	4/5	1/5
Non-Cyclic Alkyl Phosphoramides and Thionophosphoramides	1	1/1	0/1	1/1
Organic Diselenides and Ditellurides	1	1/1	1/1	0/1
Peroxyacyl Nitrates	1	1/1	1/1	0/1
Quinoxaline-Type 1,4-Dioxides	2	2/2	2/2	0/2
Organic Azides	1	1/1	1/1	0/1
Specific 5-Substituted Uracil Derivatives	1	1/1	1/1	0/1
Bleomycin and Structurally Related Chemicals	2	2/2	2/2	0/2
Short-Chain Alkyltin and Alkylgermanium Halides	1	1/1	1/1	0/1
Perfluoroalkyl Hypohalites	1	1/1	1/1	0/1
Propyne Derivatives	1	1/1	1/1	0/1
Haloepoxides and Halooxetanes	3	3/3	3/3	0/3

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	2175	1825/2175	1047/1825	778/1825

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 for CA and MNT by OASIS.***

Endpoint-Specific ***DNA alerts for AMES by OASIS*** includes structural boundaries which are defined based on chemicals with positive experimental data for Ames test (i.e. a specific endpoint). These structural boundaries could be considered as alerts for Ames mutagenicity, because they include complete set of structural and parametric boundaries providing sufficiency for eliciting positive Ames effect. These alerts are supported by empirical toxicity data. Because of that endpoint-specific DNA binding profilers are suitable for making direct SAR predictions. On the other hand, they also could be used for more precise definition of analogues for read-across.

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 alerts for AMES 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. N-methylol derivatives – new category is added
4. Specific Acetate Esters - modified - prohibition (expressed with NOT) for nitro group and four-membered lactones
5. Amino Anthraquinones - modified– a mask for nitro group is added
6. Fused-Ring Primary Aromatic Amines - modified - a mask is added
7. 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
8. Nitro Azoarenes and p-Substituted Azobenzenes – new name - the category has a new name and a new query for p-Substituted Azobenzenes is added
9. Nitroaniline Derivatives – modified - a mask is added
10. Nitrophenols, Nitrophenyl Ethers and Nitrobenzoic Acids – modified - addition of masks
11. Sulfonates and Sulfates - modified - enumeration is added with O-, N and C{ar} atoms
12. Quinoxaline-Type 1,4-Dioxides - modified – a mask forbidding fused aromatics is added
13. Four- and Five-Membered Lactones - modified- prohibition (expressed with NOT) for anhydrides
14. Haloalkanes Containing Heteroatom - modified - explicit H-atoms are added
15. Haloalcohols – modified - in query #2, I-atom is removed - equally to general mechanistic profiler
16. Perfluoroalkyl Hypohalites – new category is added
17. Propyne Derivatives– new category is added
18. Haloepoxides and Halooxetanes– 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).