About section of a profiler
Name of the profiler
in vitro mutagenicity (Ames test) alerts by ISS
Developer; Donator; date; version
Developer: ISS team (Romualdo Benigni, Cecilia Bossa, Olga Tcheremenskaia) ***Donator:*** Istituto Superiore di Sanità (ISS), Rome, Italy ***Version:*** 2.3 December 2016
Relevance/Applicability to endpoint(s)
This profiler is based on the Mutagenicity module of the software Toxtree. It works as a decision tree for estimating *in vitro* (Ames test) mutagenicity, based on a list of 43 structural alerts (SAs). The SAs for mutagenicity are molecular functional groups or substructures known to be linked to the mutagenic activity of chemicals. As one or more SAs embedded in a molecular structure are recognised, the system flags the potential mutagenicity of the chemical. The present list of alert is relevant for the investigation of chemicals genotoxicity, *via* DNA adducts formation.
Relevance/Applicability to particular chemical classes
This profiler is applicable to chemicals containing at least a SA from the list. Absence of alerts in the molecular structure may be associated to absence of potential reactivity in the Ames test, or may be due to a lack of mechanistic knowledge. Therefore, the 'No structural alert' flag is not equivalent to a negative prediction.
Approach used to develop the profiler - Concise but informative description of:
The present list of SAs has been compiled building upon existing knowledge on mechanism of action of genotoxic chemicals. The initial list has been then refined taking into account also experimental Ames test results (ISSSTY database).
Literature references: Benigni R, Bossa C (2011) Mechanisms of chemical carcinogenicity and mutagenicity: a review with implications for predictive toxicology. Chem Rev 111: 2507–2536 ISSTOX, Chemical Toxicity Databases: http://www.iss.it/ampp/?lang=1&id=233&tipo=7
Summary description of profiles/alerts within the profiler
Positive predictivities shown in the table below are calculated by applying the profiler to the database "Bacterial mutagenicity ISSSTY" (QSAR Toolbox 4.0). This database contains results of Ames test on over 7000 chemicals (around 3500 positive calls and 2800 negatives). Chemicals with an 'Inconclusive' result were discarded from the present calculation. In the analysis, a chemical is defined as 'positive', if at least one alert is present in its molecular structure. The calculation of the predictivity of each individual alert is based on the 'overall' Ames test calls. The "overall" positivity has been assigned to a chemical if at least one positive Ames test result have been found in the literature, irrespective of the test conditions such as strain or metabolic activation, as it is explained in the accompanying documentstion of the ISSSTY database (http://www.iss.it/ampp/?lang=1&id=233&tipo=7).

Profiler Alerts	Number of chemicals with the alert	Number of chemicals positive in the Ames test	Positive Predictivity of the alert
9,10-dihydrophenanthrenes	66	57	0.86
Acyl halides	30	23	0.77
Aliphatic azo and azoxy	30	23	0.77
Aliphatic halogens	402	269	0.67
Aliphatic N-nitro group	10	9	0.90
Alkenylbenzenez	42	9	0.21
Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid	66	37	0.56
Alkyl and aryl N-nitroso groups	151	129	0.85
Alkyl carbamate and thiocarbamate	35	20	0.57
Alkyl hydroperoxides	18	14	0.78
Alkyl nitrite	7	7	1.00
alpha,beta-unsaturated aliphatic alkoxy group	18	15	0.83
alpha,beta-unsaturated carbonyls	322	156	0.48
Anthrones	117	91	0.78
Aromatic diazo	144	96	0.67
Aromatic mono-and dialkylamine	136	87	0.64
Aromatic N-acyl amine	120	72	0.60
Aromatic nitroso group	49	42	0.86
Aromatic ring N-oxide	22	11	0.50
Azide and triazene groups	89	85	0.96
Coumarins and Furocoumarins	42	20	0.48
DNA Intercalating agents with a basic side chain	14	12	0.86
Epoxides and aziridines	383	270	0.70
Flavonoids	9	4	0.44
Fluorinated quinolines	16	12	0.86
Haloalkene cysteine S-conjugates	8	8	1.00
Halofuranones	20	19	0.95
Heterocyclic Polycyclic Aromatic Hydrocarbons	422	367	0.87
Hydrazine	197	125	0.63
Hydroxamic acid derivatives	6	4	0.67
Isocyanate and isothiocyanate groups	19	7	0.37
Monohaloalkene	17	9	0.53

N-acyloxy-N-alkoxybenzamides	25	25	1.00
N-aryl-N-acetoxyacetaamides	5	4	0.80
Nitro-aromatic	895	749	0.84
N-methylol derivatives	7	2	0.29
Polycyclic Aromatic Hydrocarbons	652	540	0.83
Primary aromatic amine,hydroxyl amine and its derived esters	699	498	0.72
Propiolactones or propiosultones	5	4	0.80
Pyrrolizidine alkaloids	13	3	0.23
Quinones	180	132	0.73
S or N mustard	40	32	0.80
Simple aldehyde	110	49	0.45
Steroidal estrogens	4	0	0.00
Triphenylimidazole and related	8	8	1.00
Xanthones, Thioxanthones, Acridones	37	30	0.81

Counter category: No alert found

Similar to other profilers

This profiler is similar to the two general mechanistic profilers: ***DNA binding by OECD*** and ***DNA binding by OASIS.*** However, the structural alerts in the endpoint specific profiler are more specific than the general mechanistic ones and are focused on chemistry associated with binding to DNA especially causing Ames mutagenicity effect.

This profiler is similar also to the Endpoint specific profiler: ***DNA alerts for AMES, MN and CA by OASIS.*** The outcome of the two profilers may differ because of different construction and because they were developed taking into account different factors that may modulate the reactivity associated with each functional group.

In contrast to the OASIS and OECD profilers, hierarchically organized with mechanistic domains and associated mechanistic alerts, ISS profiler is a list of Structural Alerts, each associated with a mechanistic explanation.

This profiler is partially overlapping with the lists ***in vivo mutagenicity (Micronucleus) alerts by ISS*** and ***Carcinogenicity (genotox and nongenotox) alerts by ISS***, given the partial overlapping among the Molecular Initiating Events of the endpoints.

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 ***In vitro mutagenicity (Ames test) alerts by ISS*** 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:

•Included three additional categories: “Alkenylbenzenes”, “Pyrrolizidine alkaloids” and “Steroidal estrogens”

•“Aliphatic azo and azoxy” – C atoms connected to N=N can be any aliphatic instead of one in sp3 hybridisation

•“Aromatic mono- and dialkylamines” – Added a rule related to fused aromatic structures with a sulfonic acid group as substituent

•“*alpha,beta*-unsaturated carbonyls”- changed in the help-file description

•“Azide and triazene groups” - Difference in charge of N atoms in N=N=N structure

Disclaimer
This profiler is intended for the prediction of the mutagenicity potential of chemicals, as detected by the Ames test. For its construction, it can be used to the assessment of the genotoxicity of DNA-reactive chemicals. While the presence of an alert (or more) is indicative of potential DNA-reactivity, the absence of any alert does not necessarily means absence of such reactivity. Expert knowledge could be necessary to finalize the data gap filling procedure. 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).