About section of a profiler
Name of the profiler
Carcinogenicity (genotox and nongenotox) alerts by ISS
Developer; Donator; date; version
Developer: ISS team (Romualdo Benigni, Cecilia Bossa, Olga Tcheremenskaia) ***Donator:*** Institute for Health and Consumer Protection, Joint Research Centre - European Commission, Ispra, Italy; Istituto Superiore di Sanità (ISS), Rome, Italy ***Version:*** 2.3 December 2016
Relevance/Applicability to endpoint(s)
This profiler is an expanded and updated version of the correspondent module originally implemented in the software Toxtree. It works as a decision tree for estimating carcinogenicity, based on a list of 55 structural alerts (SAs). Out of them, 35 derive from the Toxtree module and 20 are newly derived. Most of the new SAs are relative to nongenotoxic carcinogenicity, whereas the SAs in the initial list mainly coded genotoxic carcinogenicity. The SAs for carcinogenicity are molecular functional groups or substructures known to be linked to the carcinogenic activity of chemicals. As one or more SAs embedded in a molecular structure are recognised, the system flags the potential carcinogenicity of the chemical. The present list of alert is relevant for the investigation of chemicals genotoxic and nongenotoxic carcinogenicity.
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 carcinogenic reactivity, 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 carcinogenic chemicals. The list has been partially refined taking into account experimental results on long-term carcinogenicity bioassay on rodents (ISSCAN and ISSBIOC databases, http://www.iss.it/ampp/?lang=1&id=233&tipo=7).
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 • Benigni R, Bossa C, Tcheremenskaia O. (2013) Nongenotoxic Carcinogenicity of Chemicals: Mechanisms of Action and Early Recognition through a New Set of Structural Alerts. Chem Rev. 2013 May 8;113(5):2940-57. • 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 "Carcinogenicity&mutagenicity ISSCAN" (QSAR Toolbox 4.0). This database contains results of Ames test on over 1100 chemicals (around 700 positive calls and 400 negatives). 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 'summary' carcinogenicity call. The 'summary' carcinogenicity has been assigned to chemicals found to be carcinogenic in at least one experimental group (rats/mice, male/female), irrespective of the experimental conditions (*e.g.* duration, route of administration), as it is explained in the accompanying documentation of the ISSCAN 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 carcinogenicity test	Positive Predictivity of the alert
(Poly) Halogenated Cycloalkanes (Nongenotox)	18	14	0.78
1,3-Benzodioxoles (Nongenotox)	10	7	0.70
Acyl halides (Genotox)	1	1	1.00
Aliphatic azo and azoxy (Genotox)	8	7	0.88
Aliphatic halogens (Genotox)	76	52	0.68
Aliphatic N-nitro group (Genotox)	5	5	1.00
Alkenylbenzenes (Genotox)	8	7	0.88
Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid (Genotox)	15	13	0.87
Alkyl and aryl N-nitroso groups (Genotox)	120	106	0.88
Alkyl carbamate and thiocarbamate (Genotox)	7	6	0.86
Alkyl halides (Nongenotox)	13	12	0.92
Alkyl nitrite (Genotox)	1	1	1.00
alpha,beta-unsaturated aliphatic alkoxy group (Genotox)	3	3	1.00
alpha,beta-unsaturated carbonyls (Genotox)	54	31	0.57
Aromatic diazo (Genotox)	25	19	0.76
Aromatic mono-and dialkylamine (Genotox)	15	10	0.67
Aromatic N-acyl amine (Genotox)	17	12	0.71
Aromatic nitroso group (Genotox)	3	3	1.00
Aromatic ring N-oxide (Genotox)	2	2	1.00
Azide and triazene groups (Genotox)	4	2	0.50
Benzenesulfonic ethers, methylation (Nongenotox)	11	8	0.73
Coumarins and Furocoumarins (Genotox)	7	6	0.86
Dicarboximide (Nongenotox)	0		
Dimethylpyridine (Nongenotox)	0		

Epoxides and aziridines (Genotox)	27	19	0.70
Halogenated benzene (Nongenotox)	20	7	0.35
Halogenated dibenzodioxins (Nongenotox)	4	2	0.50
Halogenated PAH (naphthalenes, biphenyls, diphenyls) (Nongenotox)	11	9	0.82
Heterocyclic Polycyclic Aromatic Hydrocarbons (Genotox)	15	13	0.87
Hydrazine (Genotox)	69	57	0.83
Imidazole, benzimidazole (Nongenotox)	14	7	0.50
Indole-3-carbinol (Nongenotox)	0		
Isocyanate and isothiocyanate groups (Genotox)	5	3	0.60
Metals, oxidative stress (Nongenotox)	3	2	0.67
Monohaloalkene (Genotox)	6	5	0.83
Nitro-aromatic (Genotox)	88	63	0.72
N-methylol derivatives (Genotox)	2	2	1.00
o-phenylphenol (Nongenotox)	2	2	1.00
Pentachloro phenol (Nongenotox)	2	2	1.00
Perfluorooctanoic acid (PFOA) (Nongenotox)	0		
Phenoxy herbicides (Nongenotox)	0		
Phtalate (or buthyl) diesters and monoesters (Nongenotox)	5	3	0.60
Polycyclic Aromatic Hydrocarbons (Genotox)	9	7	0.78
Primary aromatic amine,hydroxyl amine and its derived esters (Genotox)	106	83	0.78
Propiolactones or propiosultones (Genotox)	4	4	1.00
Pyrrolizidine alkaloids (Genotox)	4	4	1.00
Quercetin type flavonoids (Nongenotox)	2	1	0.50
Quinones (Genotox)	14	12	0.86
S or N mustard (Genotox)	10	10	1.00
Simple aldehyde (Genotox)	10	9	0.90
Steroidal estrogens (Nongenotox & Genotox)	2	2	1.00
Substituted n-alkylcarboxylic acids (Nongenotox)	7	7	1.00
Substituted phenoxyacid (Nongenotox)	6	4	0.67
Thiocarbonyl (Nongenotox)	22	12	0.55
Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene (Nongenotox)	5	5	1.00

Counter category: No alert found

Similar to other profilers

This profiler is partially overlapping with the lists ***In vitro mutagenicity (Ames test) alerts***

by ISS and ***In vivo mutagenicity (Micronucleus) alerts by ISS***, given the partial overlapping between the Molecular Initiating Events of the endpoints (for what concerns genotoxic carcinogens).

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 "Name of the profiler" 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:
•"(Poly) Halogenated Cycloalkanes (nongenotoxic)" – modification of number of Halogens to be three or more
•"Aliphatic azo and azoxy (genotox)" – C atoms connected to N=N can be any aliphatic instead of one in sp3 hybridisation
•"Alkylbenzenes (genotox)" renamed to "Alkenylbenzenes (genotox)"
•"Azide and triazene groups (genotox)" - Difference in charge of N atoms in N=N=N structure
•"Imidazole, Benzimidazole (nongenotoxic)" – referring to Benzimidazole, all atoms in benzene ring are set to be C instead of including hetero
•"Perfluorooctanoic Acid (PFOA) (nongenotoxic)" –COOH group included in the SMART
•"Phenoxy Herbicides (nongenotoxic)" – addition of a rule both O atoms at the ends of the molecule not to be connected with H atom
•"Substituted n-Alkylcarboxylic Acids (nongenotoxic)" – changes in the help-file related with number of C atoms
•"Aromatic mono- and dialkylamines (genotoxic)" – Added a rule related to fused aromatic structures with a sulfonic acid group as substituent
•"*alpha,beta*-unsaturated carbonyls (genotoxic)"- changed in the help-file description

Disclaimer

This profiler is intended for the prediction of the genotoxic and non-genotoxic carcinogenicity potential of chemicals. While the presence of an alert (or more) is indicative of potential carcinogenic reactivity, the absence of any alert does not necessarily mean absence of such reactivity. Expert knowledge is necessary to finalize a 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).