ToxEraser tools

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ToxEraser tools

- Software tools for substitution, designed for specific sectors:
  - **Cosmetics**
  - **Food Contact Materials (FCM)**
  - **Solvents**

- ToxEraser suggests safer compounds as remedy to a given hazardous molecule, supporting the substitution decision making procedure

- Goal: to reduce the number of hazardous substances, improving health prevention

ToxEraser tools

Main features

- Authoritative lists of compounds with safety (regulatory) levels
- Research of substitution candidates based on structural chemical similarity (from VEGA)
- Identification of possible hazardous structural groups / alerts
- (Cosmetics) Definition and classification of functional uses

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Lists of compounds

- Systematic retrieval of information about compounds with specific information about their use from a regulatory point of view
- Harmonization of sources and labelling with different safety levels
- Different sources depending on the sector of application – focus on regulatory allowed compounds

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Lists of compounds - Cosmetics

- Existing exclusion list
  - *SIN list*
  - *Substances not allowed or restricted in cosmetics (Annexes of the Cosmetic Regulation 1223/2009)*
  - *CMR from COSING*

- Existing safer chemicals list
  - *Safer Chemical Ingredient List (SCIL)*
  - *Generally Recognized As Safe (GRAS)*
  - *Substances allowed in Cosmetics and FCM*

- Other lists
  - *CIR (Cosmetic Ingredient Review)*
  - *IFRA (International Fragrance Association)*

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Lists of compounds - Cosmetics

Classification	N° of substances
Regarded as generally safe	455
Regarded as generally safe with restrictions	111
Only commercially available	382
Only commercially available with restrictions	868
Banned in Europe	16
Banned both in Europe and US	401

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Lists of compounds – FCM

- Source for substances:
  - *ANNEX I (Commission Regulation (EU) No. 10/2011)*
  - *Safer Chemical Ingredient List (SCIL)*

- Classification: indication of the source for given compounds (Annex and/or SCIL list)

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Lists of compounds – Solvents

- Source for substances :
  - *SUSSOL (Sustainable Solvents Selection and Substitution Software) tool list*
  - *Solvent Selection Tool list from ACS GCI Pharmaceutical Roundtable (GCIPR)*
  - *Safer Chemical Ingredient List (SCIL)*
  - *SIN list*

- Classification: possible labels depending on agreement of single sources
  - Recommended
  - Problematic
  - Hazardous
  - Conflicting Assessment

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Research by similarity

- Possible candidates for substitution are searched and sorted using the chemical similarity implemented in the VEGA platform

- The structural similarity consider all the main relevant chemical feature, weighting also specific functional groups and the molecular weight of the molecules

Floris *et al. Journal of Cheminformatics* 2014, **6**:39
http://www.jcheminf.com/content/6/1/39

Journal of Cheminformatics

RESEARCH ARTICLE Open Access

A generalizable definition of chemical similarity for read-across

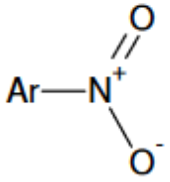
Matteo Floris[1,2†], Alberto Manganaro[3†], Orazio Nicolotti[4], Ricardo Medda[2], Giuseppe Felice Mangiatordi[4] and Emilio Benfenati[3*]

Structural Alerts

- Identification of potentially hazardous structural alerts, in the target molecule (given by the user) and in the retrieved compounds for substitution

- Example of alert, from the Benigni/Bossa ruleset

SA_27: Nitro-aromatic



Ar = Any aromatic/heteroaromatic ring

- Chemicals with ortho-disubstitution, or with an ortho carboxylic acid substituent are excluded.
- Chemicals with a sulfonic acid group (-SO3H) on the same ring of the nitro group are excluded .

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Structural Alerts

- Structural alerts for human hazard:
  - Benigni/Bossa ruleset for carcinogenicity and mutagenicity
  - ED alerts developed by IRFMN on the EU and WHO lists

- Specific alerts for cosmetics:
  - Skin Sensitization ruleset from ToxTree

- Specific alerts for solvents:
  - Aquatic toxicity alerts developed by IRFMN

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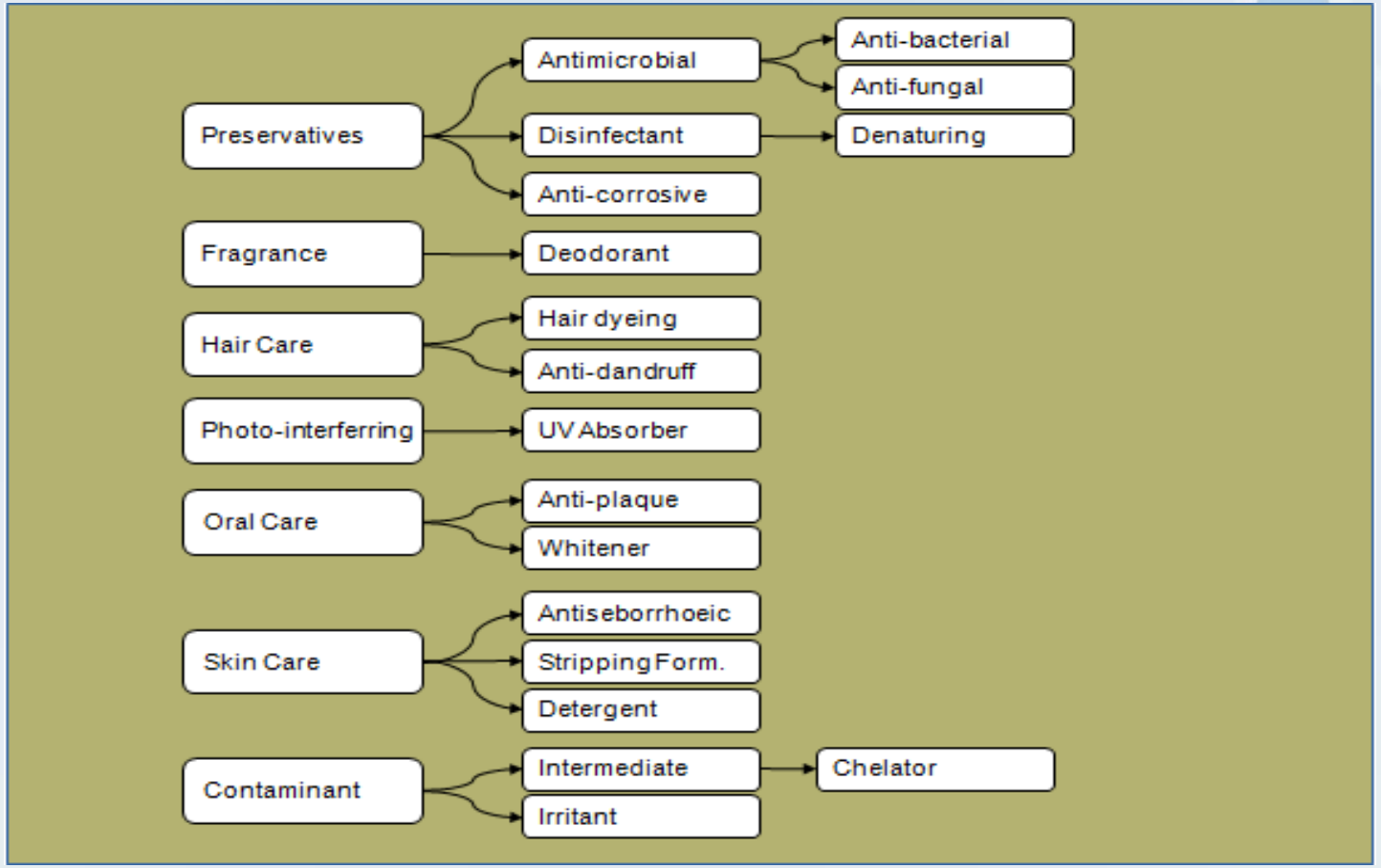
Functional uses

- Cosmetics according to their functional uses, a hierarchical ontology



Application

- ToxEraser applications have been developed as three different Java software, available for free download.
- They are standalone applications – no data sent through the internet.
- Implementation: Java (version 11 or above) standalone application, with a Graphical User Interface (GUI) based on JavaFX.
- It allows the user to provide an input molecule (as a SMILES string) and its function, and provides a PDF report with the results from the

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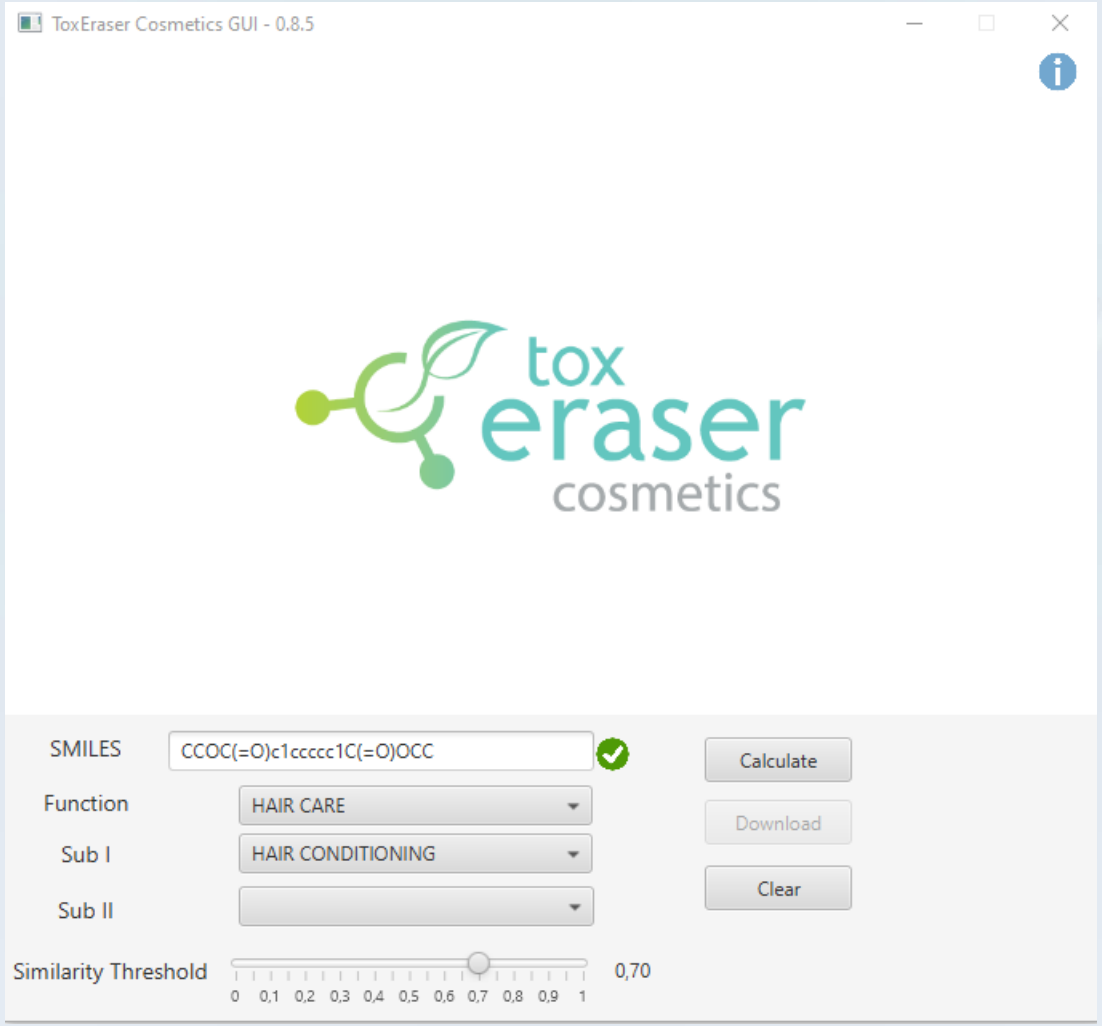
Example: Cosmetics tool



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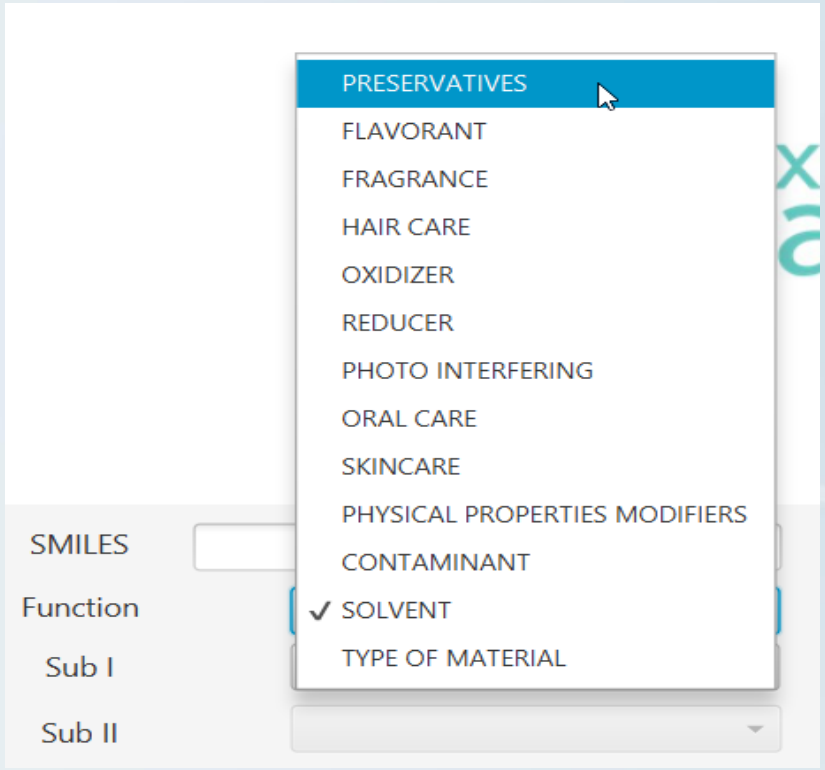
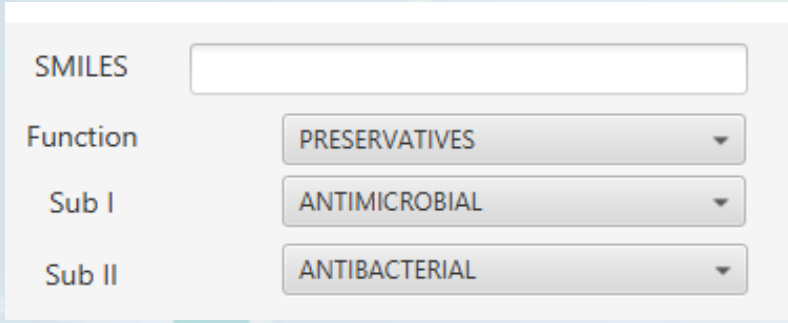
Example: Cosmetics tool





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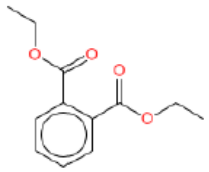
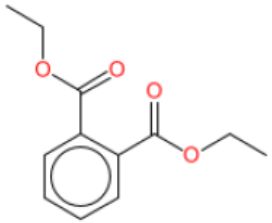
Example: Cosmetics tool



Target Compound:
CCOC(=O)c1ccccc1C(=O)OCC

Target Function:
HAIR CONDITIONING

Molecule was found in DB



Similarity Index: 1

Final Class: regarded as generally safe with restrictions

Function: DENATURANT | FILM FORMING | HAIR CONDITIONING | MASKING | PLASTICISER | SOLVENT | DENATURING ALCOHOL. VEHICLE FOR FRAGRANCE AND COSMETIC INGREDIENTS | PLASTICIZER | WETTING AGENT | FIXATIVE | DISPERSING MEDIUM | DYE CARRIER.

Molecule Name: DIETHYL PHTHALATE

CAS: 84-66-2 | 68988-18-1

SMILES: CCOC(=O)c1ccccc1C(=O)OCC

VEGA SMILES: O=C(OCC)c1ccccc1(C(=O)OCC)

INSTITUTIONAL ASSESSMENT
SIN: Diethyl phthalate (DEP) is an endocrine disruptor with thyroid and estrogenic activity, affecting several body functions and target organs including reproduction, liver and metabolism. The substance has been found in biomonitoring studies and in human urine. It is categorized as an endocrine disruptor in the EU Commission Database.
CIR: Safe as used
COSING: allowed

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Example: Cosmetics tool

2 Structural Alerts found in target molecule

SA42 Phthalate diesters and monoesters Phthalate diesters and monoesters
SA Endocrine 6 Structural alert for EC defined by the SMARTS: O(C)C(=O)c1ccccc1C(OC)=O

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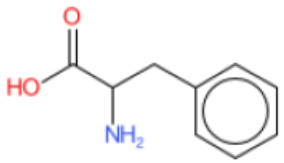
Example: Cosmetics tool

1 REGARDED AS GENERALLY SAFE compound found in DB



Similarity Index: 0,74

Final Class: regarded as generally safe

Matching Function(s): HAIR CONDITIONING

Function: HAIR CONDITIONING | MASKING | SKIN CONDITIONING

Molecule Name: PHENYLALANINE

CAS: 150-30-1 | 09/02/5297

SMILES: NC(Cc1ccccc1)C(=O)O

VEGA SMILES: O=C(O)C(N)Cc1ccccc1

INSTITUTIONAL ASSESSMENT
CIR: Safe as used
COSING: allowed