The QSAR Toolbox to support the genotoxicity assessment of chemicals: the experience of the Istituto Superiore di Sanità (Italy)

Cecilia Bossa
ISS - Environment and Health Department

ISS is the technical and scientific body of the Italian Ministry of Health and the main centre for research, control and technical-scientific advice on public health in Italy

The activity of the **Environment and Health Department** is focused on multidisciplinary research which includes the identification and characterization of environmental and social risk factors, the study of their effects on health, and risk assessment

The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of ISS

***in silico* Toxicology Unit** founded by Romualdo Benigni

Chiara Laura Battistelli, Cecilia Bossa, Alessandro Giuliani, Olga Tcheremenskaia

Development and application of computational methods in the assessment of toxicological risk

- ✓ Implementation, evaluation and development of structure-activity relationships-based methodologies (e.g., (Q)SAR, read across, grouping, AOP and IATA approaches) to support chemicals (including nanomaterials) risk assessment.
- ✓ Study of the mechanism of action of genotoxic and carcinogenic chemicals; coding of structural determinants for chemicals toxicity (genotoxicity/carcinogenicity).
- ✓ Development of statistical and Systems-Biology models
- ✓ Analysis and standardization of experimental data, creation of chemical relational databases on toxicological endpoints.
- ✓ The group is actively committed in promoting the QSAR Toolbox (*e.g.*, through the donation of ISS databases and profilers and participation in the OECD QSAR Toolbox Management Group)

Institutional tasks

- ✓ REACH related activity
- ✓ National remediation sites related activity

Research activity

- ✓ Applicability of in silico models for predicting the genotoxicity of pesticides
- ✓ Japan DGM/NIHS 1st Ames/QSAR international collaborative project

REACH related activity

ISS supports the Member State Competent Authority in substance evaluation

(Community Rolling Action Plan - CoRAP) and dossier evaluation

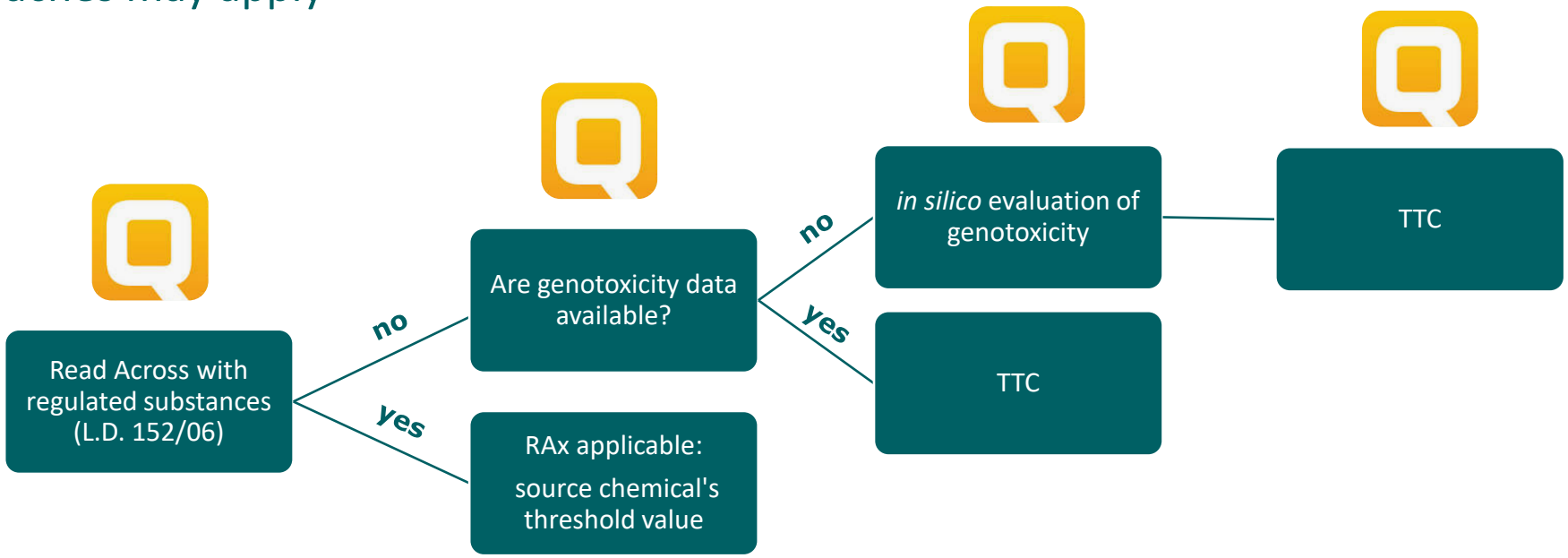
→ Evaluation of QSARs, Read across and Grouping approaches (genotoxicity/carcinogenicity)

- Structure inspection, chemical identity verification (including CAS-SMILES relation)
- Experimental data availability
- Toxicological profiling (*in silico*)
- Insights on the mechanism of action
- Search for analogues
- Verification of RAx elements, Chemical Category consistency, QSAR results
- Data matrix generation, in tabular form (working basis)

National remediation sites related activity

ISS is asked to express opinions on the definition of the threshold concentration of contamination (substances not included in the Legislative Decree 152/06).

In the presence of a non-regulated chemical, lacking sufficient toxicological information, *in silico* approaches may apply



Institutional tasks

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Research activity

- ✓ Applicability of in silico models for predicting the genotoxicity of pesticides
- ✓ Japan DGM/NIHS 1st Ames/QSAR international collaborative project

Applicability of *in silico* models for predicting the genotoxicity of pesticides
(EFSA funded project - OC/EFSA/PRAS/2016/01)

- Characterization of the structural changes resulting from metabolic or degradation processes of the active substances and evaluation of their impact on the genotoxicity potential

EXTERNAL SCIENTIFIC REPORT

APPROVED: 12 March 2019

doi:10.2903/sp.efsa.2019.EN-1598

Evaluation of the applicability of existing (Q)SAR models for predicting the genotoxicity of pesticides and similarity analysis related with genotoxicity of pesticides for facilitating of grouping and read across

Romualdo Benigni*, Chiara Laura Battistelli**, Cecilia Bossa**, Alessandro Giuliani**, Elena Fioravanzo***, Arianna Bassan***, Mojca Fuart Gatnik***, James Rathman****, Chihae Yang****and Olga Tcheremenskaia**

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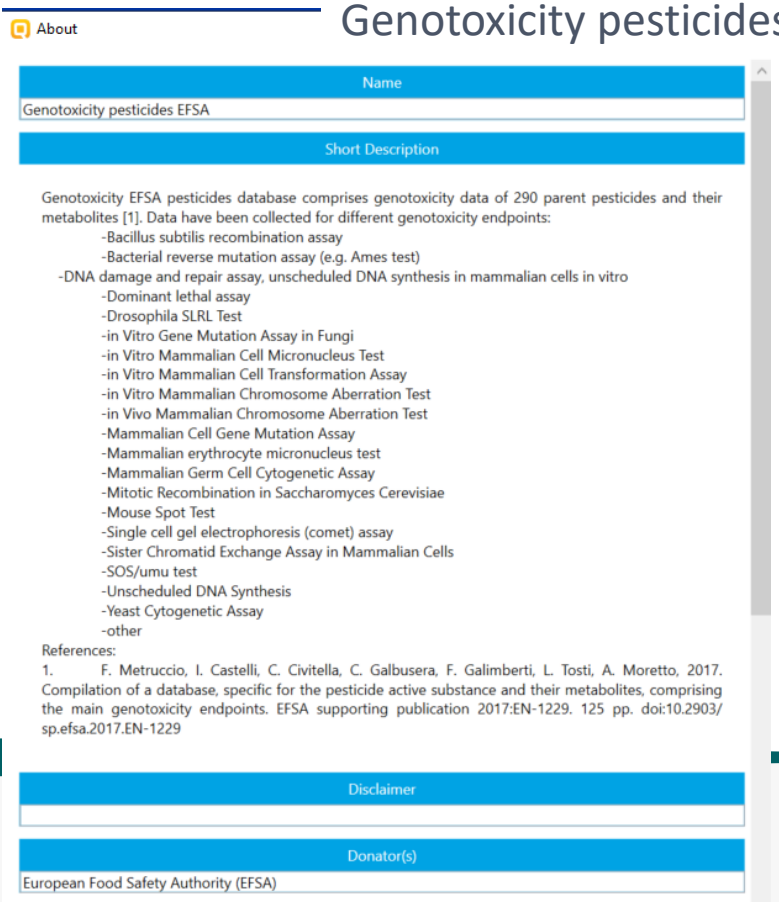
Evaluation of the applicability of existing (Q)SAR models for predicting the genotoxicity of pesticides and similarity analysis related with genotoxicity of pesticides for facilitating of grouping and read across: An EFSA funded project

Romualdo Benigni[a,*], Rositsa Serafimova[b], Juan Manuel Parra Morte[b], Chiara Laura Battistelli[c], Cecilia Bossa[c], Alessandro Giuliani[c], Elena Fioravanzo[d], Arianna Bassan[d], Mojca Fuart Gatnik[d], James Rathman[e], Chihae Yang[e], Aleksandra Mostrag-Szlichtyng[e], Oliver Sacher[c], Olga Tcheremenskaia[c]



About

Genotoxicity pesticides EFSA

Name

Genotoxicity pesticides EFSA

Short Description

Genotoxicity EFSA pesticides database comprises genotoxicity data of 290 parent pesticides and their metabolites [1]. Data have been collected for different genotoxicity endpoints:

-Bacillus subtilis recombination assay
-Bacterial reverse mutation assay (e.g. Ames test)
-DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells in vitro
-Dominant lethal assay
-Drosophila SLRL Test
-in Vitro Gene Mutation Assay in Fungi
-in Vitro Mammalian Cell Micronucleus Test
-in Vitro Mammalian Cell Transformation Assay
-in Vitro Mammalian Chromosome Aberration Test
-in Vivo Mammalian Chromosome Aberration Test
-Mammalian Cell Gene Mutation Assay
-Mammalian erythrocyte micronucleus test
-Mammalian Germ Cell Cytogenetic Assay
-Mitotic Recombination in Saccharomyces Cerevisiae
-Mouse Spot Test
-Single cell gel electrophoresis (comet) assay
-Sister Chromatid Exchange Assay in Mammalian Cells
-SOS/umu test
-Unscheduled DNA Synthesis
-Yeast Cytogenetic Assay
-other

References:

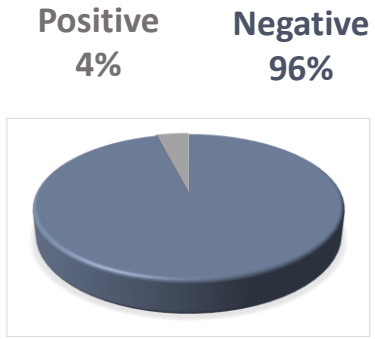
1. F. Metruccio, I. Castelli, C. Civitella, C. Galbusera, F. Galimberti, L. Tosti, A. Moretto, 2017. Compilation of a database, specific for the pesticide active substance and their metabolites, comprising the main genotoxicity endpoints. EFSA supporting publication 2017:EN-1229. 125 pp. doi:10.2903/sp.efsa.2017.EN-1229

Disclaimer

Donator(s)

European Food Safety Authority (EFSA)

***in vitro* bacterial reverse mutation assay (Ames test)**



~ 900 chemicals

1/3 active substances

2/3 metabolites

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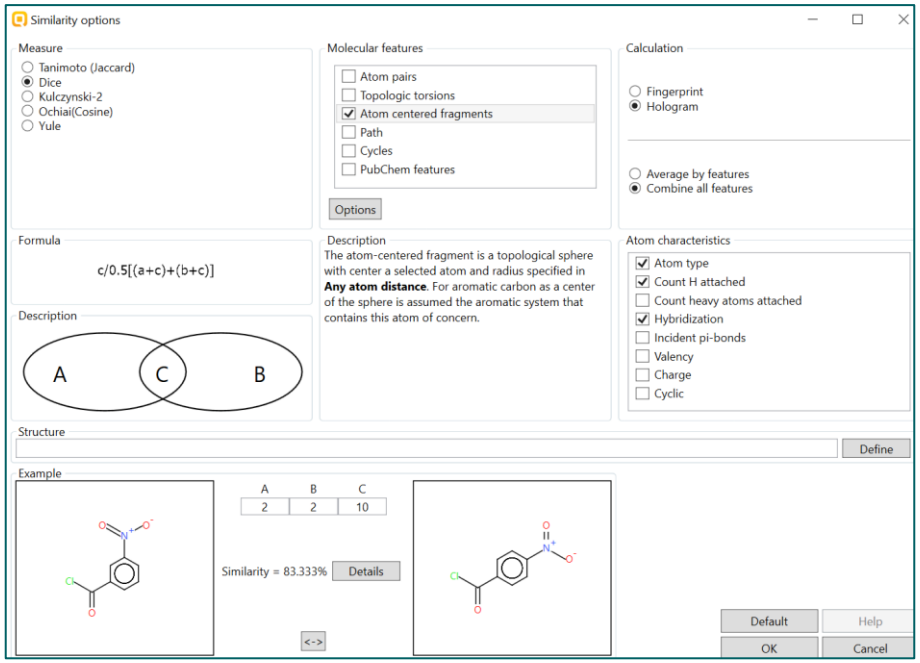
Analysis of the structural changes (in terms of functional groups) that occur in the transformation from the parent substance to the metabolites

✓ Focus on the metabolites which maintain the core structure of the parent

→ **similarity analysis**



We selected 319 AS/metabolite pairs with similarity ≥ 70%

Analysis of the structural changes (in terms of functional groups) that occur in the transformation from the parent substance to the metabolites

- ✓ Focus on the metabolites which maintain the core structure of the parent
  → **similarity analysis**

- ✓ Characterize the structural features that change more frequently in the transformation from the parent to the metabolites
  → **functional group analysis**

Analysis of the structural changes (in terms of functional groups) that occur in the transformation from the parent substance to the metabolites

✓ Characterize the structural features that change more frequently in the transformation from the parent to the metabolites

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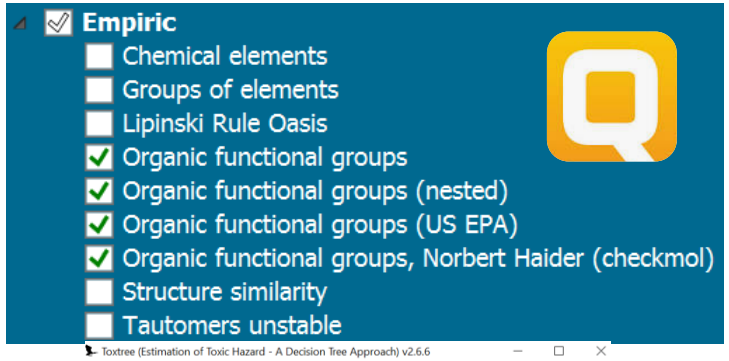
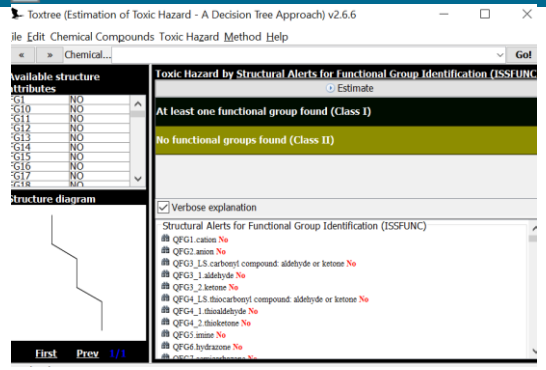
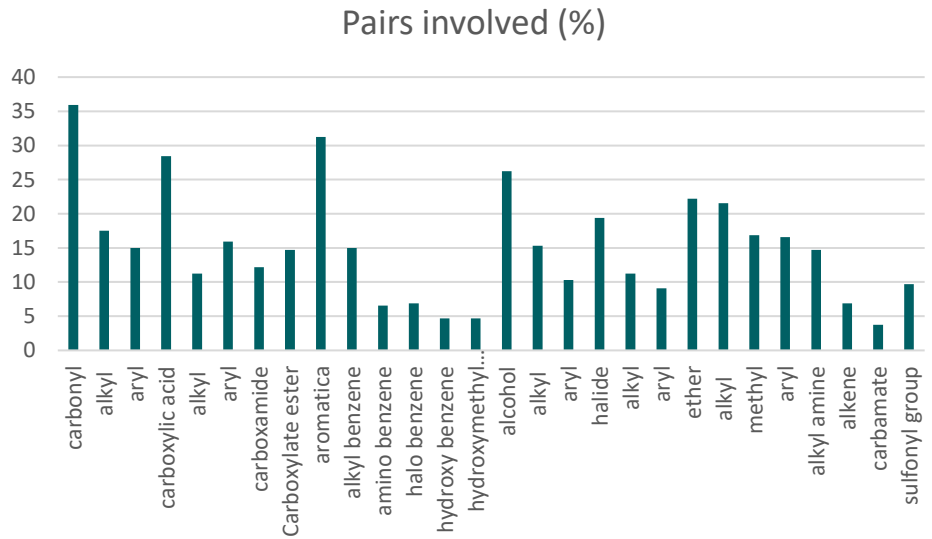


Toolbox profilers



Toxtree – ISSFUNC profiler



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Analysis of the structural changes (in terms of functional groups) that occur in the transformation from the parent substance to the metabolites

- ✓ Focus on the metabolites which maintain the core structure of the parent
  → **similarity analysis**

- ✓ Characterize the structural features that change more frequently in the transformation from the parent to the metabolites
  → **functional group analysis**

- ✓ Evaluate the impact of the structural changes on the mutagenicity potential
  → **structure-activity relationships analysis**

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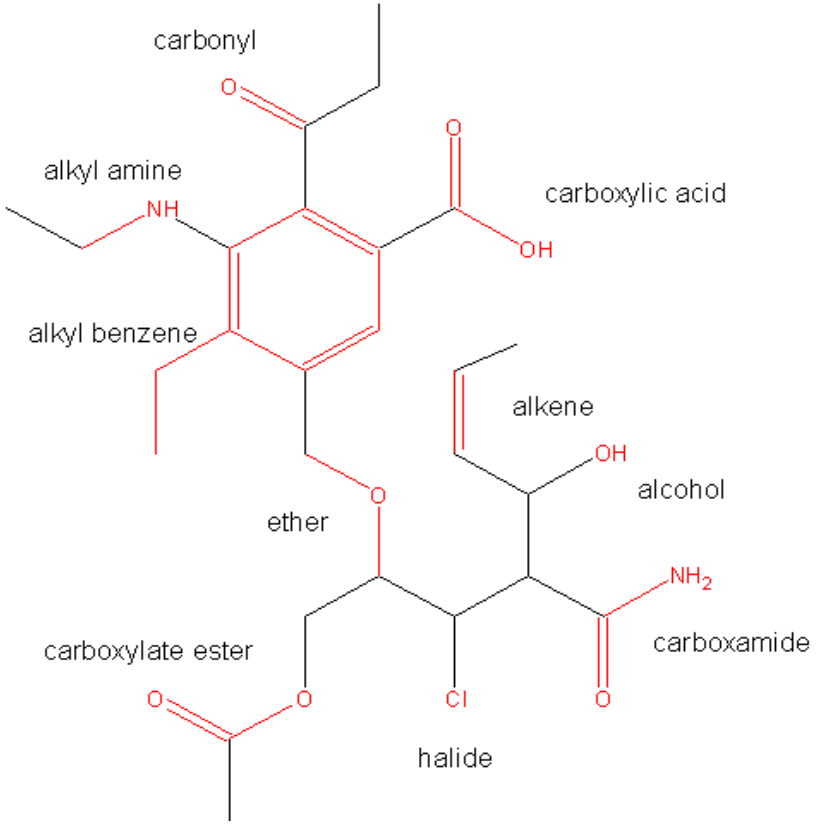
Analysis of the structural changes (in terms of functional groups) that occur in the transformation from the parent substance to the metabolites

✓ Evaluate the impact of the structural changes on the mutagenicity potential

→ **structure-activity relationships analysis**



Non-toxifying structural changes in Parent / Metabolite pairs with high similarity

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Improvement of QSAR profiler for predicting Ames mutagenicity
1st Ames/QSAR international collaborative project

Mutagenesis, 2019, 34, 3–16
doi:10.1093/mutage/gey031
Original Manuscript

OXFORD

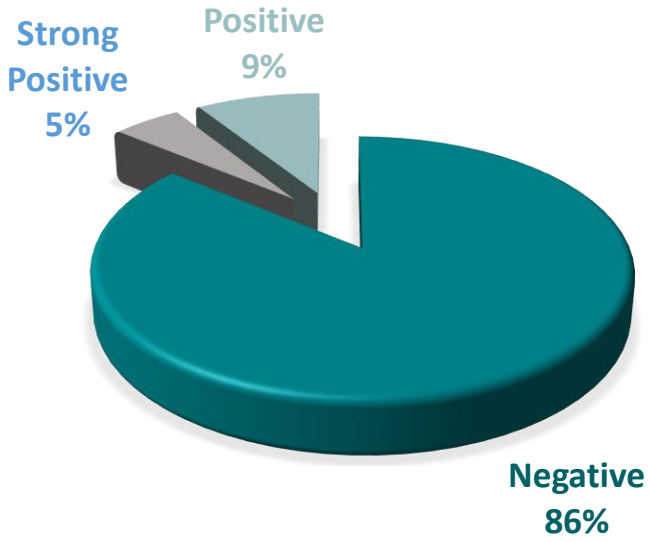
Original Manuscript

Improvement of quantitative structure–activity relationship (QSAR) tools for predicting Ames mutagenicity: outcomes of the Ames/QSAR International Challenge Project

Masamitsu Honma*, Airi Kitazawa, Alex Cayley[1], Richard V. Williams[1], Chris Barber[1], Thierry Hanser[1], Roustem Saiakhov[2], Suman Chakravarti[2], Glenn J. Myatt[3], Kevin P. Cross[3], Emilio Benfenati[4], Giuseppa Raitano[4], Ovanes Mekenyan[5], Petko Petkov[5], Cecilia Bossa[6], Romualdo Benigni[6,7], Chiara Laura Battistelli[6], Alessandro Giuliani[6], Olga Tcheremenskaia[6], Christine DeMeo[8], Ulf Norinder[9,10], Hiromi Koga[11], Ciloy Jose[11], Nina Jeliazkova[12], Nikolay Kochev[12,13], Vesselina Paskaleva[13], Chihae Yang[14], Pankaj R. Daga[15], Robert D. Clark[15] and James Rathman[14,16]

- Promoted by the Japan National Institute of Health Sciences (DGM/NIHS), aimed at improving the reliability and applicability of QSAR models for predicting Ames mutagenicity, by the analysis of new Ames test results

More than 12,000 chemicals tested according to the OECD TG471 guideline

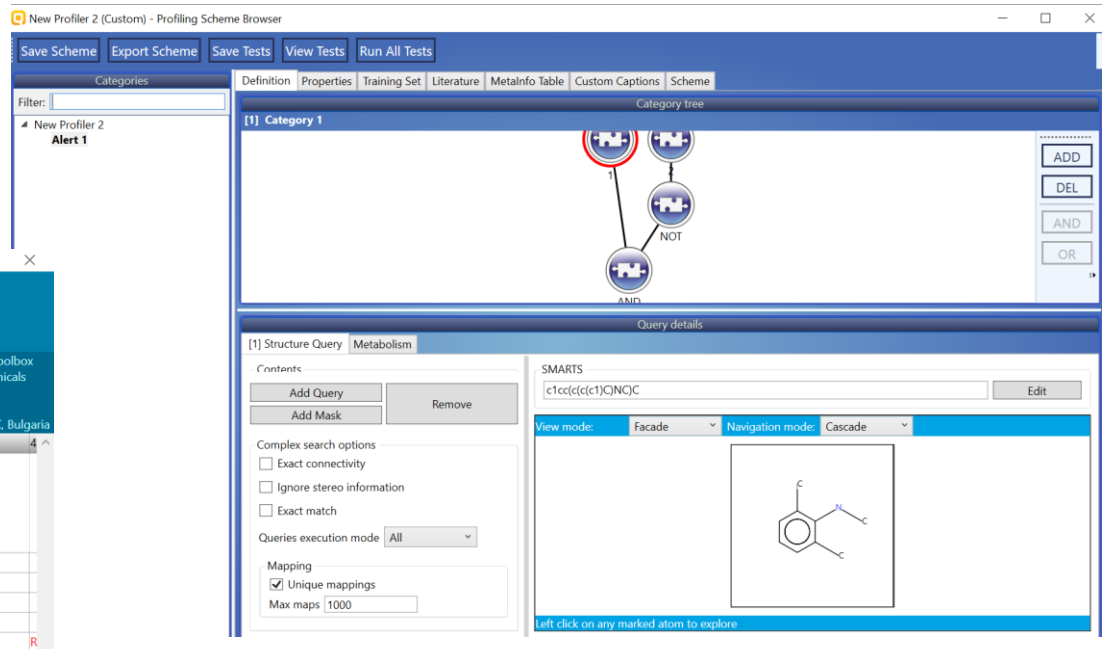


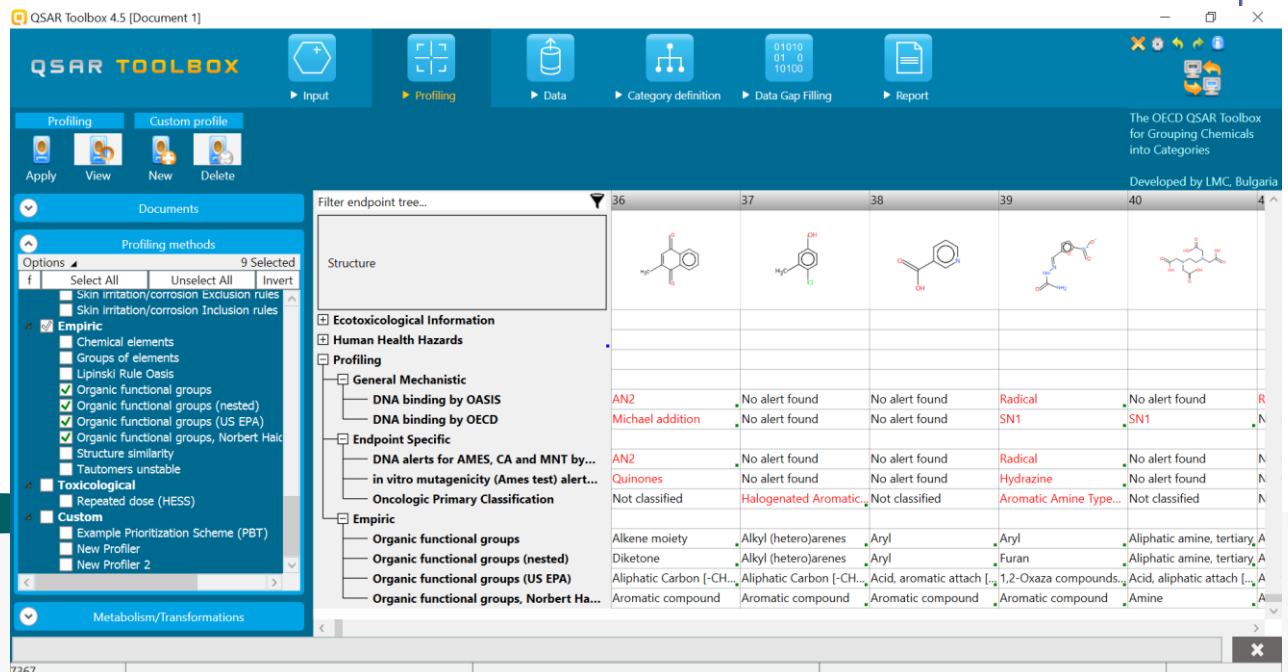
Improvement of QSAR profiler for predicting Ames mutagenicity

→ in vitro mutagenicity (Ames test) alerts by ISS – Toxtree /QSAR Toolbox profiler

- Chemical structure inspection
- Functional groups analysis
- Toxicological profiling (*in silico*)
- Insights on the mechanism of action

QSAR Toolbox Custom Profile functionality





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Thank you for your attention!