Prioritization of emerging pollutants on the basis of chemical structure

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INTRODUCTION & OBJECTIVES

The prioritization of hazardous chemicals is a useful procedure for the identification of critical substances and the optimization of experiments. This procedure became of particular relevance within the EU-REACH regulation, which encourages the minimization of animal testing also by the use of alternative *in vitro* and *in silico* methods. Among these methods quantitative structure-activity relationships (QSARs) can predict missing data for the unknown activities and properties necessary to prioritize existing or not yet synthesized chemicals. The prioritization of four classes of emerging pollutants (brominated flame retardants, fragrances, perfluorinated compounds and (benzo)triazoles) is one of the topics of the FP7 European project CADASTER. The prioritization applied to CADASTER chemicals was crucial to focus the experimental design on critical substances on the basis of their chemical structure and potential ecotoxicological hazard.

The aim of this poster is to summarize the prioritization activity performed within the CADASTER project, also by applying "ad hoc" QSAR/QSPR models developed so far for the four classes of compounds under investigation.

FINAL GOAL of CADASTER

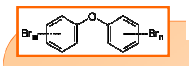
to exemplify the integration of information, models and strategies for carrying out hazard and risk assessments for four classes of emerging pollutants:

- Brominated Flame Retardants
- Perfluorinated Compounds
- Fragrances
- Triazoles / benzotriazoles

METHODS

Different prioritization procedures were applied to over 1000 chemicals by combining, through different approaches (similarity analysis, multivariate ranking methods, factorial design), the structural information, encoded in theoretical molecular descriptors, and the data (experimental or predicted) available for different toxicological and ecotoxicological endpoints. Chemicals belonging to the ECHA pre-registration list were also studied in the prioritizations. Priority compounds were suggested for focusing the experiments executed by other CADASTER partners.

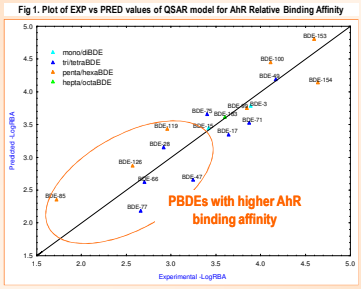
BROMINATED FLAME RETARDANTS (BFRs)

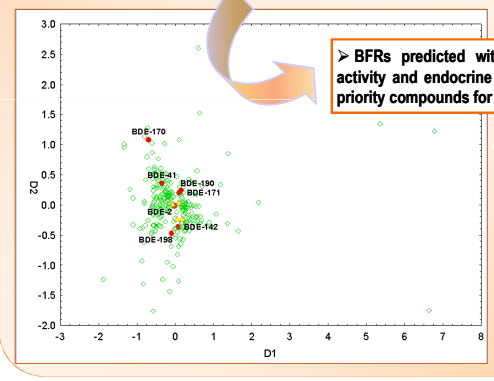


➢ QSAR models developed for several endpoints related to DIOXIN-LIKE activity (AhR RBA, EROD induction, AhR agonism) and ENDOCRINE DISRUPTION potency (ER agonism, PR antagonism, T4-TTR competition, E2SULT inhibition) [1,2]

➢ Predictions and applicability domain for 243 BFRs (e.g. PBDEs, OH- and CH_3- PBDE metabolites, TBBPA analogs, bromo phenols, etc...)

Fig 1. Plot of EXP vs PRED values of QSAR model for AhR Relative Binding Affinity





➢ BFRs predicted with higher activity for both dioxin-like activity and endocrine disruption potency were suggested as priority compounds for the experimental testing.

243 BFRs

11 BFRs prioritized

Fig 2. Multidimensional Scaling (MDS) plot based on molecular descriptors selected in the developed QSAR models.
Prioritized BFRs (highlighted in the plot) cover a wide structural domain and are representative of the BFR chemical space.

PERFLUORINATED COMPOUNDS (PFCs)

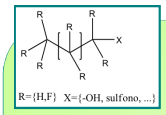
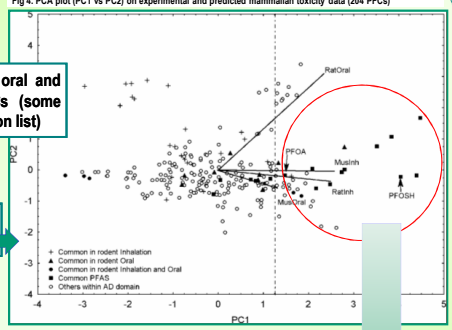
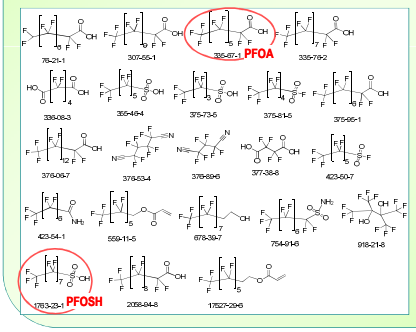


Fig 4. PCA plot (PC1 vs PC2) on experimental and predicted mammalian toxicity data (204 PFCs)



➢ QSAR models developed for mammalian oral and inhalation toxicity [4,5] applied to 376 PFCs (some chemicals included in the ECHA pre-registration list)

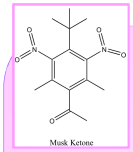
➢ PCA analysis based on experimental and predicted data (compounds within AD only)



➢ 22 long chain PFCs were identified as the most toxic for all the modelled endpoints and suggested for experimental testing

Fig 5. Structures of the 22 PFCs prioritized PFCs

FRAGRANCES



➢ QSAR models developed for mammalian ACUTE TOXICITY (LD_{50} oral) and CYTOTOXICITY (EC_{50} NADH oxidase and EC_{50} $\Delta\psi m$) [3] were applied to 79 fragrances

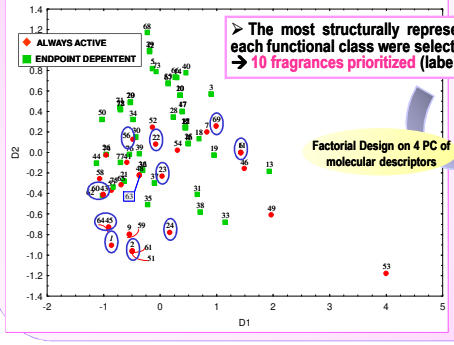
➢ 28 fragrances were identified as always active ("AA") for all the modeled endpoints

Tab 1. Always active (AA) fragrances

AHTN(tonalide,tetralide,fixolide)	Benzyl cinnamate
Celestolide, Crysolide (ADBI)	Cinnamyl benzoate
HHCB (Galaxolide)	Hexylcinnamaldeyde
OTNE	Phenethyl cinnamate
Traseolide (ATII)	α-amylcinnamyl alcohol
Musk ambrette	Acetyl cedrene
Musk moskene	Methyl dihydrojasmonate
Musk tibetene	p-t-bucinal
AHMI Phantolide	Benzyl salicylate
DPMI Cashmeran	Hexyl salicylate
AETT Versalide	Triclosan
Ethylene Brassylate	Benzyl Benzoate
Ethylene Dodecanedioate	4-t-butyl cyclohexyl acetate
Muscone	Cyclopentadecanolide

MDS based on molecular descriptors

Fig 3



➢ The most structurally representative compounds for each functional class were selected → 10 fragrances prioritized (labeled in Fig. 3 and Tab. 1)

Factorial Design on 4 PC of molecular descriptors

➢ 16 groups of structurally similar compounds

➢ For each fragrance prioritized, a list of alternative compounds was suggested for experimental testing

TRIAZOLES & BENZO-TRIAZOLES (B-TAZs)

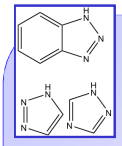
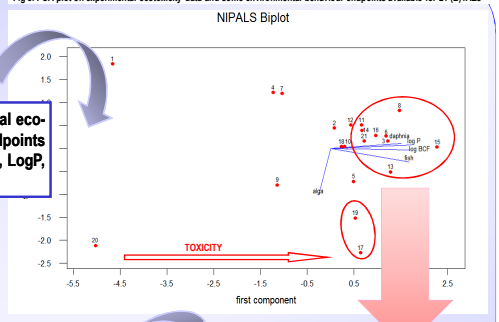


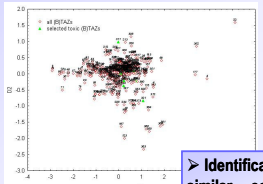
Fig 5. PCA plot on experimental ecotoxicity data and some environmental behaviour endpoints available for 21 (B)TAZs



➢ Experimental data available for several eco-toxicity and environmental behavior endpoints (i.e. EC_{50} Algae, EC_{50} Daphnia, LC_{50} fish, LogP, BCF) were analyzed by PCA

Most toxic and bioaccumulative (B)TAZs for the aquatic environment

Fig 6. MDS plot based on PCs of molecular descriptors of 386 (benzo)triazoles.



➢ Identification of most structurally similar compounds among 386 (B)TAZs without experimental data (some of them included in the ECHA pre-registration list)

MDS +K-ANN

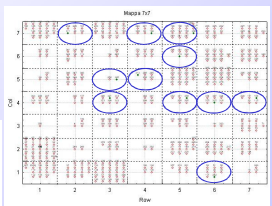


Fig 7. Kohonen maps based on PCs of molecular descriptors of 386 (benzo)triazoles. Cells containing 11 active (B)TAZs and their structurally similar compounds are highlighted with blue circles.

➢ 23 (B)TAZs prioritized for experimental testing

Financial support, given by European Union through the project CADASTER (FP7-ENV-2007-1-212668), is gratefully acknowledged (www.cadaster.eu)

CAse studies on the Development and Application of in Silico Techniques for Environmental hazard and Risk assessment

REFERENCES

[1] Papa, E.; Kovarich, S.; Gramatica, P., *Chem. Res. Toxicol.* (2010) 23, 946-954.
[2] Kovarich, S.; Papa, E.; Gramatica, P., *J Haz. Mat.* (2011) 190 (1-3), 106-112.
[3] Papa, E.; Luini, M.; Gramatica, P. *SAR QSAR Environ. Res.* (2009) 20, 767–779.
[4] Bhhatarai, B.; Gramatica, P. , *Molecular Diversity* (2011) 15, 467-476.
[5] Bhhatarai, B.; Gramatica P., *Chem. Res. Toxicol.* (2010) 23, 528-539.