Benign by design approach for more sustainable chemicals: prioritization of chemicals of environmental concern by QSAR modelling in QSARINS-Chem

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Principle 4: Design Safer (Benign) Chemicals

Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment

Principle 10: Design for Degradation

Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

BENIGN by Structural DESIGN using QSAR

QSAR for synthesis of sustainable chemicals

The HAZARD is an inherent property of a chemical

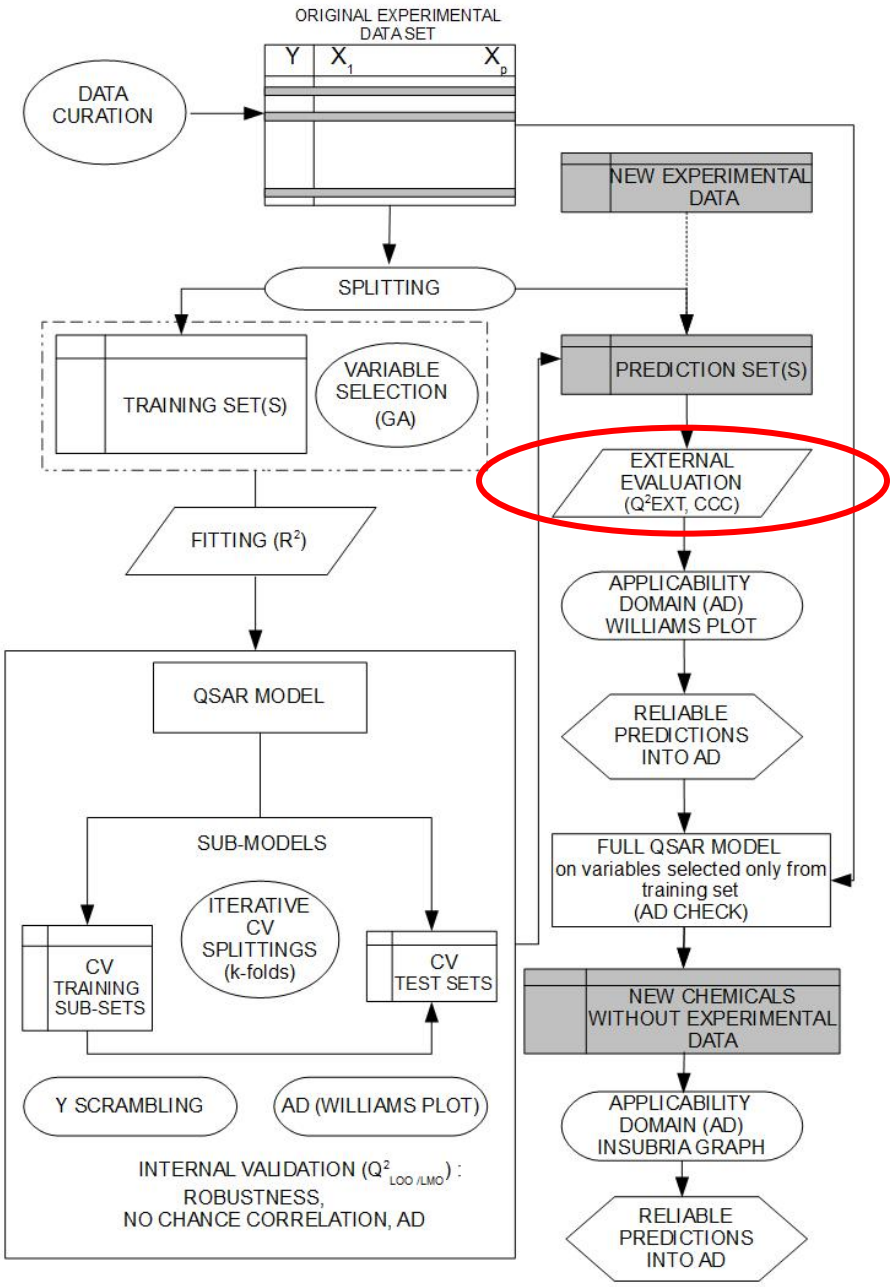
A chemical has the potentiality to be dangerous included in its MOLECULAR STRUCTURE

EXPLOIT AVAILABLE KNOWLEDGE!

A recognized harmful behaviour of a chemical must be taken into consideration to avoid similar concerns for new chemicals.

From QSAR-based screening: Priority Lists of the most hazardous chemicals can be proposed

AVOID SYNTHESIS of REGRETTABLE CHEMICALS !



Free licence request in http://www.qsar.it

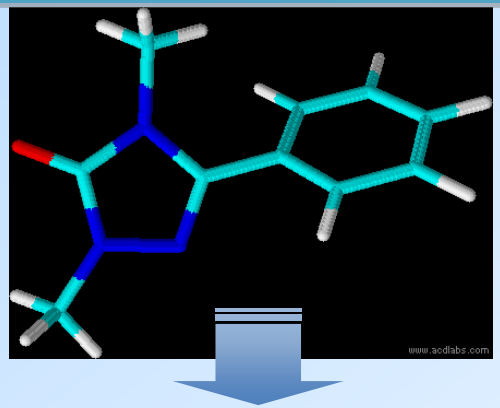
P.Gramatica et al.

J. Computational Chemistry (Software News and Updates)

34, 2121-2132, 2013.
35, 1036-1044, 2014.

MODELING in QSARINS: not «PUSH a BUTTON»

- Molecular structures are drawn and minimized by the semi-empirical method AM1 (HYPERCHEM software, hin files), and converted into SMILES or MOL files (Open Babel)



CAS	AMW	Sv	Ss	Mv	Me	Ms
000050-29-3	12.66	21.69	45.81	0.77	1.03	2.41
000050-30-6	12.73	11.22	33.89	0.75	1.06	3.08
000050-31-7	15.03	11.92	37.67	0.79	1.09	3.14
000050-32-8	7.89	23.59	37.33	0.74	0.98	1.87
000051-28-5	10.83	11.14	49	0.66	1.1	3.77
000051-44-5	12.73	11.22	33.89	0.75	1.06	3.08
000055-38-9	8.98	19.38	35.81	0.63	1.01	2.24
000055-63-0	10.77	11.67	60.83	0.56	1.14	4.06
000056-23-5	30.76	5	17.69	1	1.21	3.54
000056-38-2	9.1	19.71	49.31	0.62	1.03	2.74
000057-15-8	11.83	9.6	24.83	0.64	1.05	3.1
000057-74-9	17.07	19.79	46.81	0.82	1.07	2.6
000058-89-9	16.16	13.79	32.67	0.77	1.07	2.72
000058-90-2	17.84	11.11	32.78	0.85	1.1	2.98
000059-50-7	8.91	10.6	23.11	0.66	1.01	2.57
000060-29-7	4.94	7.5	10.5	0.5	0.98	2.1
000060-51-5	9.55	14.17	31.97	0.59	1.02	2.66

- Mono- , bi-, three-dimensional descriptors are calculated using PaDEL (free on line)
- Multiple linear regression (MLR) performed by Ordinary Least Squares (OLS) method
- Variable selection by Genetic Algorithm (GA)
- Validation by many statistical parameters.
- Various plots, also for Applicability Domain.

Chemicals of Environmental Concern (CEC)

- Persistent Organic Pollutants: from 12 «legacy» POPs
- Persistent BioaccumulativeToxics (PBTs)

CADASTER EU-Project

- Emerging pollutants: Flame Retardants (FRs), Perfluorinated (PFC), Personal Care Products (PCPs)

PCPs and Pharmaceuticals, together named PPCPs

Screening of POPs and PBTs

COMBINED APPROACH: Multivariate Analysis by PCA + QSAR

Two PCA were made on:
1. Half-lives in different environmental media for POPs
2. PBT properties

PC1: New Macro- Variables
1. GLOBAL Half-Life Index – GHLI
2. PBT Index

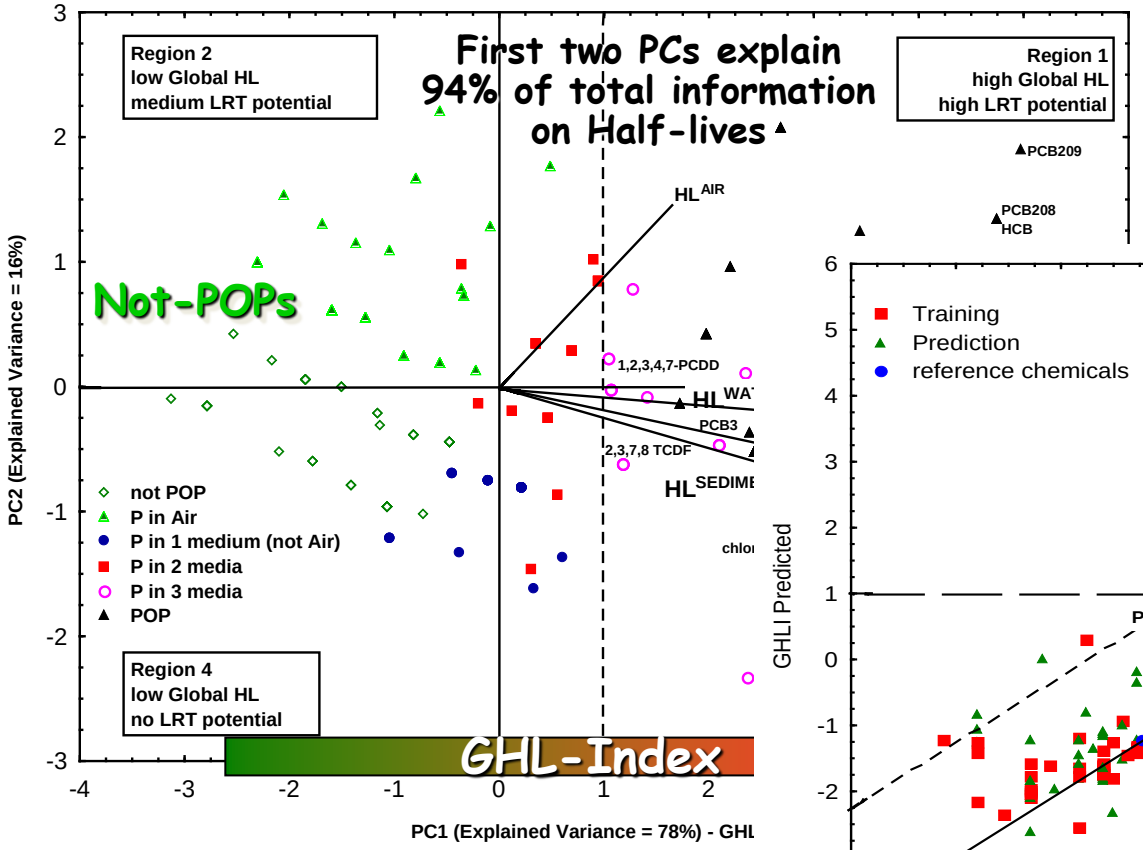
QSAR Models
MLR -OLS in QSARINS

Predictive Tools for Screening and Prioritization of potentially high concern chemicals, based on their **cumulative properties**

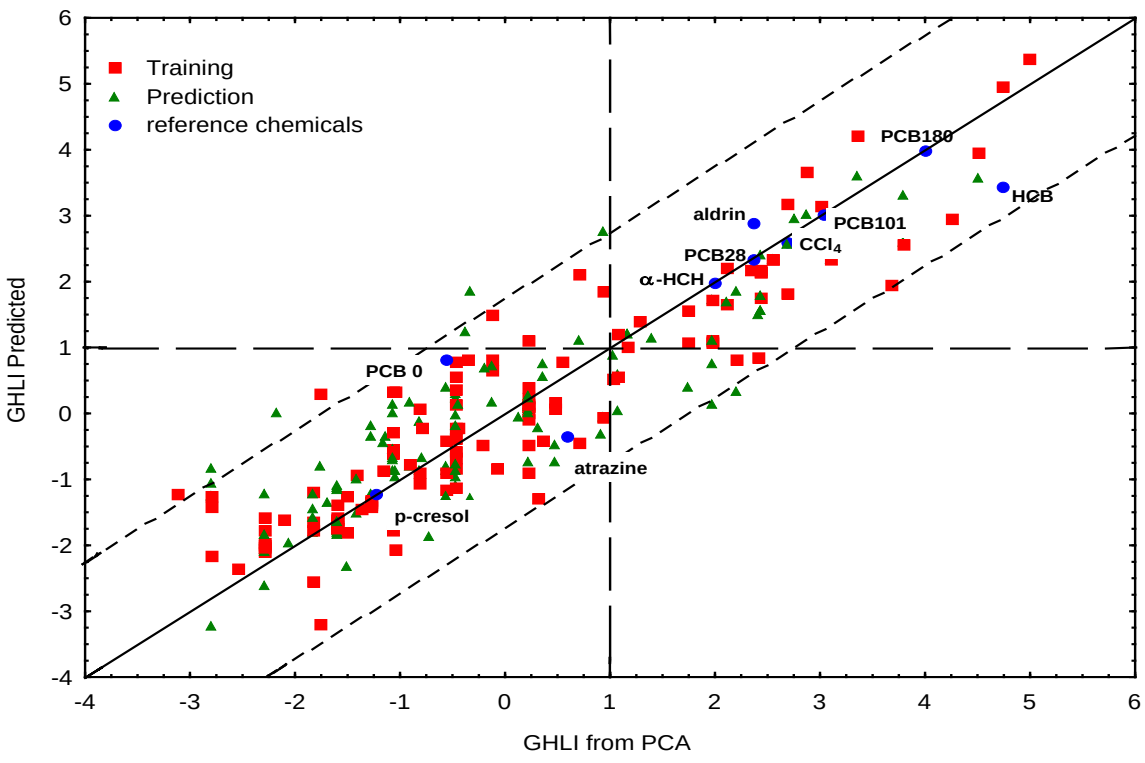
P. Gramatica
Chemometric Methods and Theoretical Molecular Descriptors in Predictive QSAR Modeling of the Environmental Behaviour of Organic Pollutants,
Ch. 12 in *Recent Advances in QSAR Studies* , Springer-Verlag, 2009

Screening of POPs: Global Half Life Index - GHLI

P. Gramatica, E. Papa, *Environ. Sci & Technol.* 41, 28, 2007.



$n_{tr.}$ = 125 R^2 = 0.85
Q^2_{LOO} = 0.83 RMSE=0.76
$n_{pr.}$ = 125 Q^2_{EXT} = 0.79
RMSEP=0.78




Environ. Sci. Technol.

Screening and Ranking of POPs for Global Half-Life: QSAR Approaches for Prioritization Based on Molecular Structure

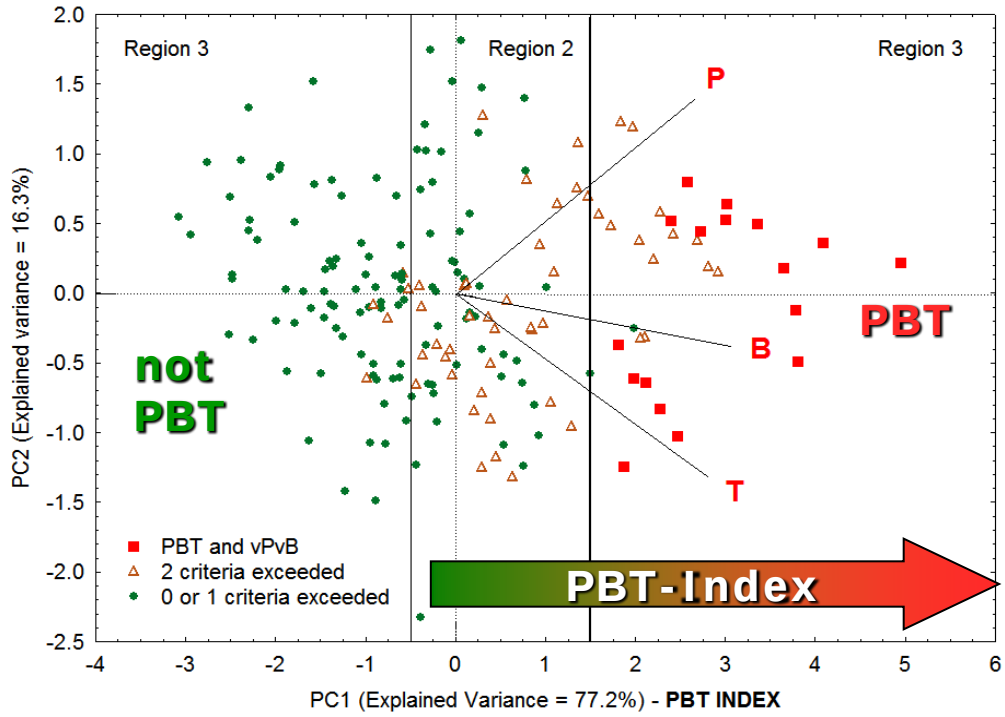
PAOLA GRAMATICA* AND ESTER PAPA

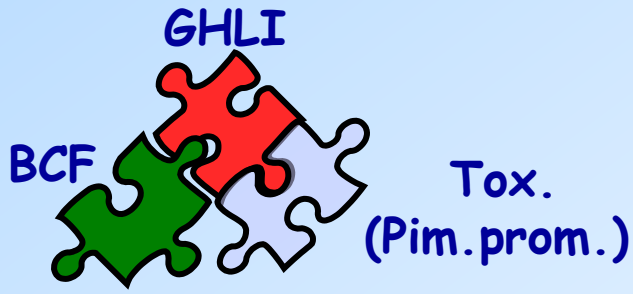
QSAR MODEL

GHL Index

Y= -3.12 +0.33 XOv+5.1 Mv-0.32 MAXDP-0.61 nHDon-0.5 CIC0-0.61 O-060

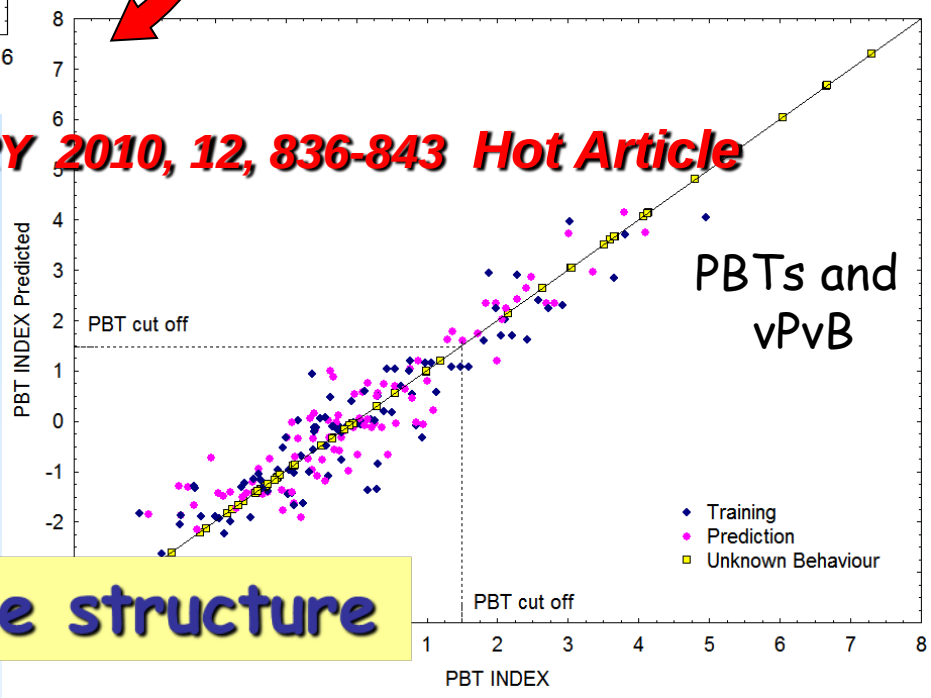
Screening of PBTs: QSAR model of PBT Index





Global Index of Persistence Bioaccumulation and Toxicity

QSAR-Model



E.Papa, P. Gramatica, *GREEN CHEMISTRY 2010, 12, 836-843 Hot Article*

PBT Index =-1.25 + 0.63nX +0.21nBM - 0.39 nHDon - 0.12 MAXDP

ntr=94; R2 = 0.88; Q2 = 0.86; $RMSE_T$=0.53;
npred=93; Q2ext = 0.87; $RMSE_P$=0.55

PBT HAZARD inherent in the structure

PBT Assessment and Prioritization by Consensus Modeling

Environment International 77 (2015) 25–34

Contents lists avail

2015, *77*, 25-34

Environment International

journal homepage: www.elsevier.com/locate/envint

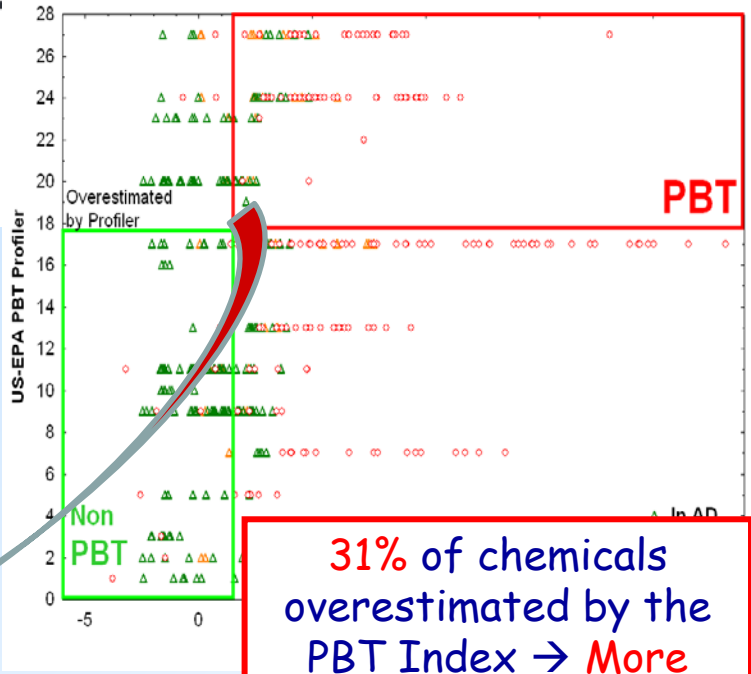
PBT assessment and prioritization by PBT Index and consensus modeling: Comparison of screening results from structural models

Paola Gramatica *, Stefano Cassani, Alessandro Sangion

4412 chemicals screened by Insubria PBT Index and US-EPA PBT Profiler → Consensus Approach (>80% agreement)

1313 chemicals identified as PBTs by Consensus: PRIORITY LIST of SVHC

Agreement graph



31% of chemicals overestimated by the PBT Index → More Precautionary

Screening of New Brominated Flame Retardants (NBFRs) and OrganoPhosphorous FR (OPFRs) by PBT Index

Journal of Hazardous Materials 306 (2016) 237–246

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Are some "safer alternatives" hazardous as PBTs? The case study of new flame retardants☆

2016, *306*, 237

Paola Gramatica*,[1], Stefano Cassani, Alessandro Sangion

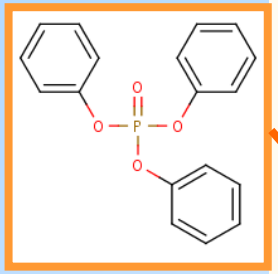
PBT Index highlights, from the design, that:

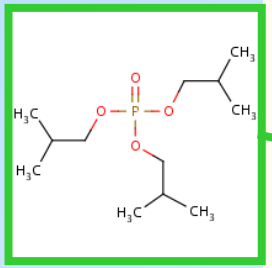
Some «safer alternatives» are not so safe:

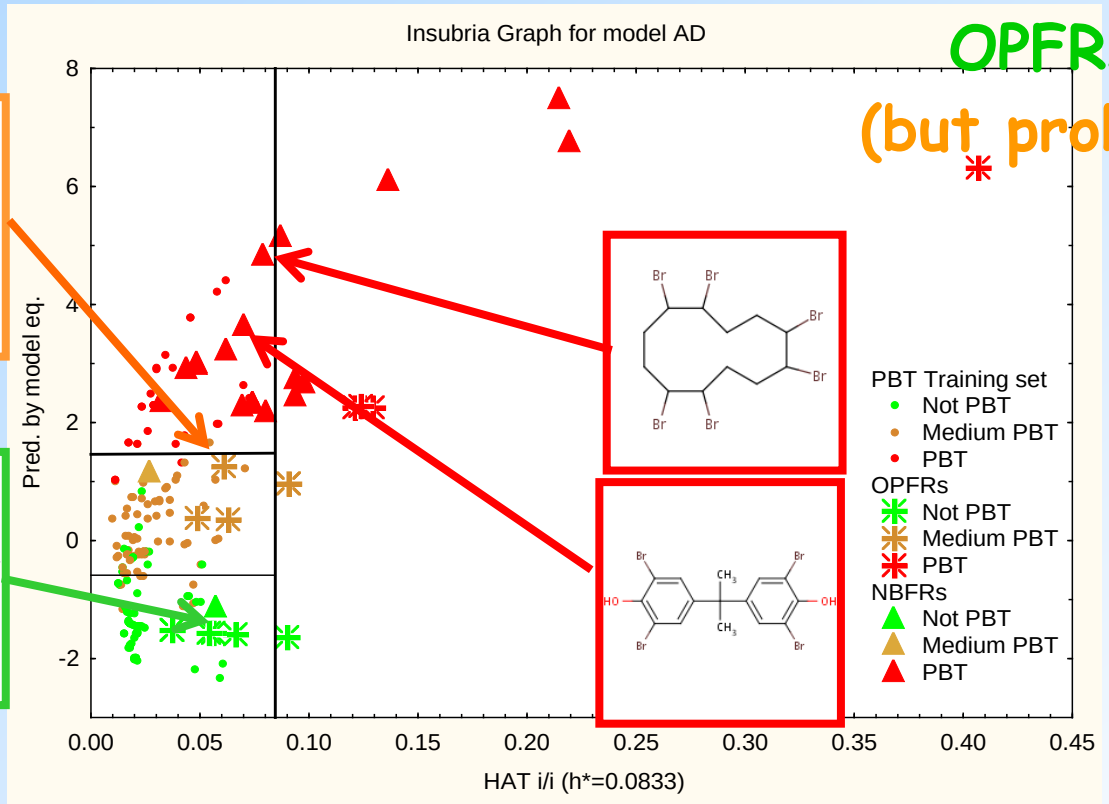
NBRFs are mainly PBTs

OPFRs are safer

(but probably not all…)







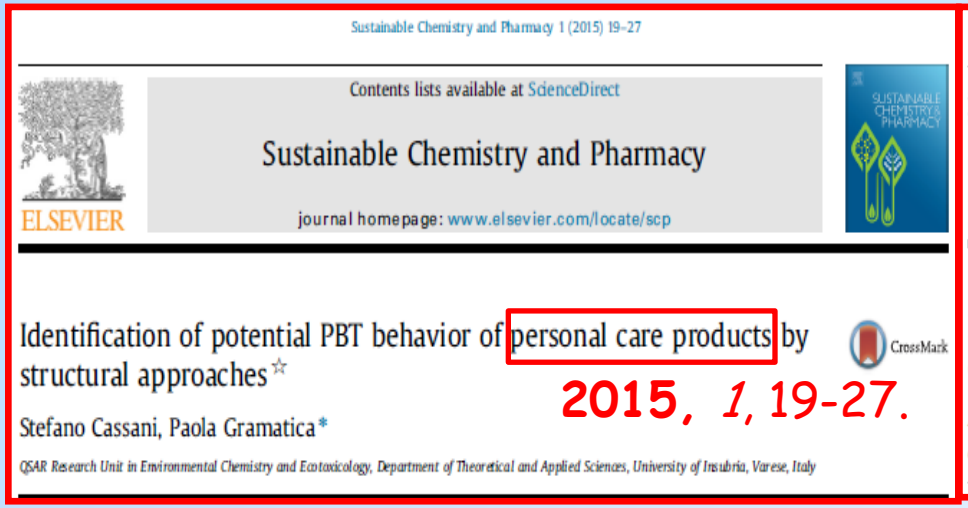
Applicability Domain (AD) of QSARINS PBT Index model

PBT behaviour of Pharmaceuticals and PCPs (PPCPs)

Comparison and consensus of two different modeling approaches for the PBT assessment

Insubria PBT Index
- Cumulative index for P, B and T, inherent to chemical structure (QSARINS)

US-EPA PBT Profiler
- Separate predictions for P, B and T


Sustainable Chemistry and Pharmacy 1 (2015) 19–27

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

journal homepage: www.elsevier.com/locate/scp

Identification of potential PBT behavior of personal care products by structural approaches ☆

Stefano Cassani, Paola Gramatica *

QSAR Research Unit in Environmental Chemistry and Ecotoxicology, Department of Theoretical and Applied Sciences, University of Insubria, Varese, Italy

2015, *1*, 19-27.


Environmental Research 147 (2016) 297–306

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

PBT assessment and prioritization of contaminants of emerging concern: Pharmaceuticals ☆

Alessandro Sangion, Paola Gramatica *

QSAR Research Unit in Environmental Chemistry and Ecotoxicology, Department of Theoretical and Applied Sciences, University of Insubria, Varese, Italy

2016, *147*, 297-306.

> 500 Personal Care Products

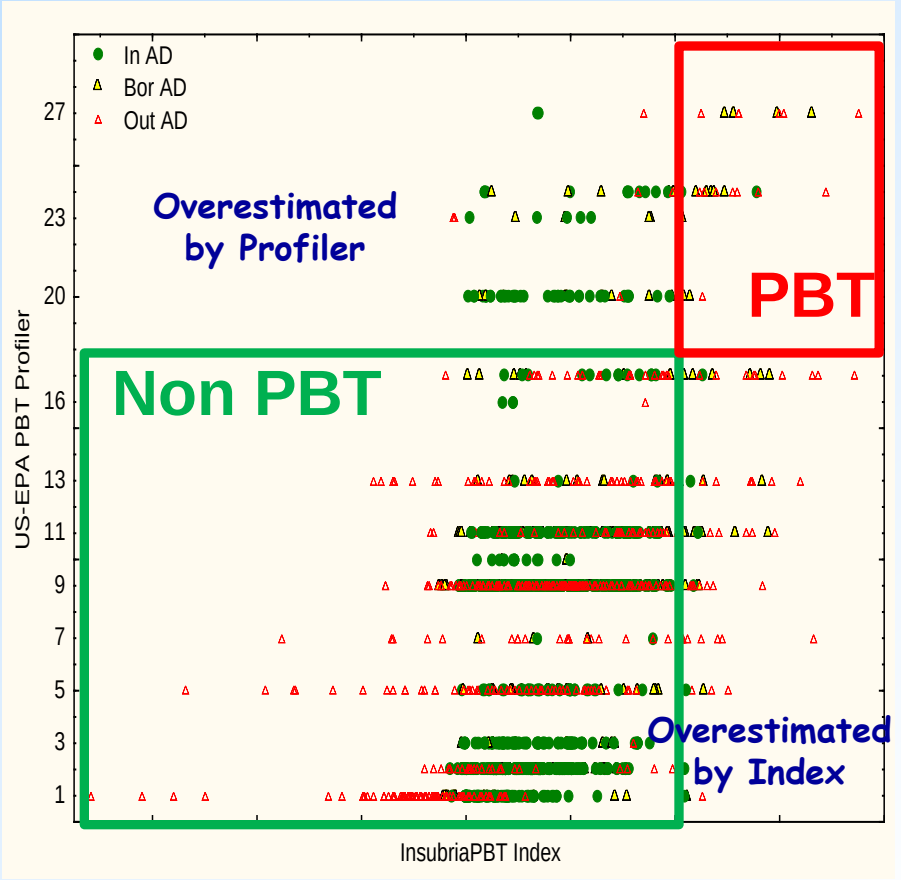
> 1200 Pharmaceuticals

Screening of PPCPs for PBT Behaviour

	all	%
Agreement	1570	87
Overestimated by Profiler	75	4
Overestimated by Index	156	9

Insubria PBT Index more precautionary

Agreement graph



chemicals labelled according to the AD

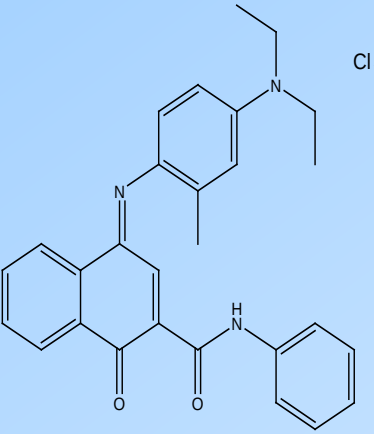
Consensus approach

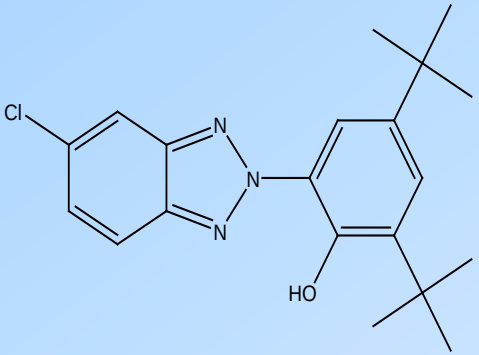
	Interp	Extrap	All
non-PBTs in agreement	1095	432	1527
PBTs in agreement	28	15	43

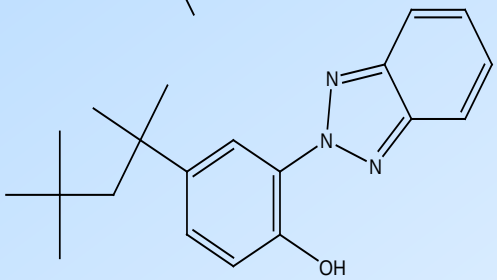
Priority List:
8 PCPs and 35 pharmaceuticals

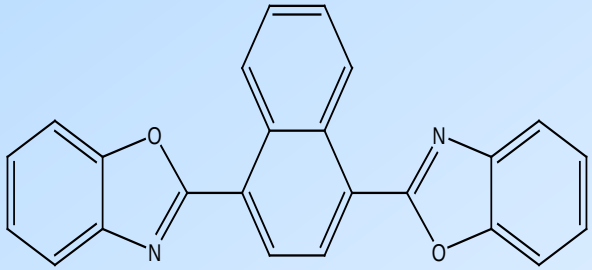
Priority List of PCPs potentially PBTs

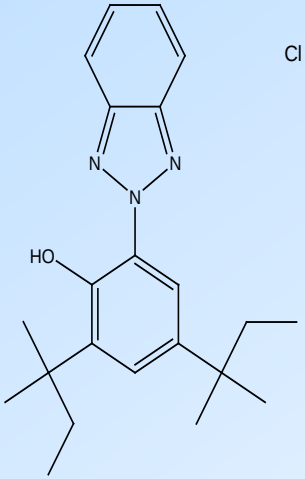
8 PCPs were predicted as potential PBT by consensus: they are mainly benzotriazoles, used as UV-filters in Sun- Screeners.

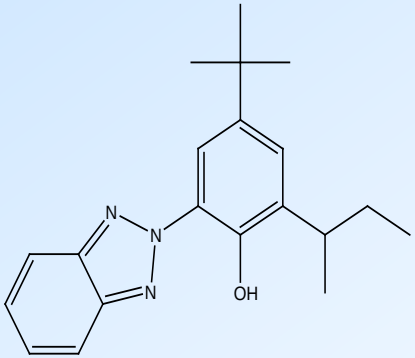


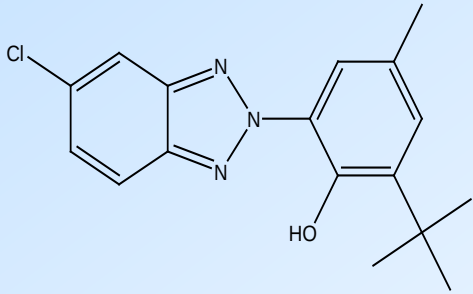


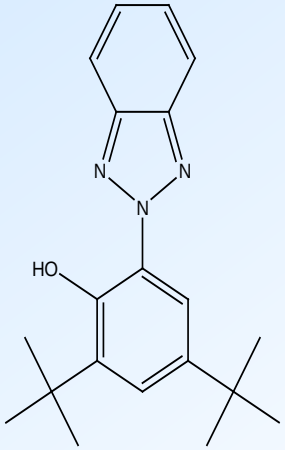












Aquatic toxicity of PCPs and Pharmaceuticals (PPCPs)

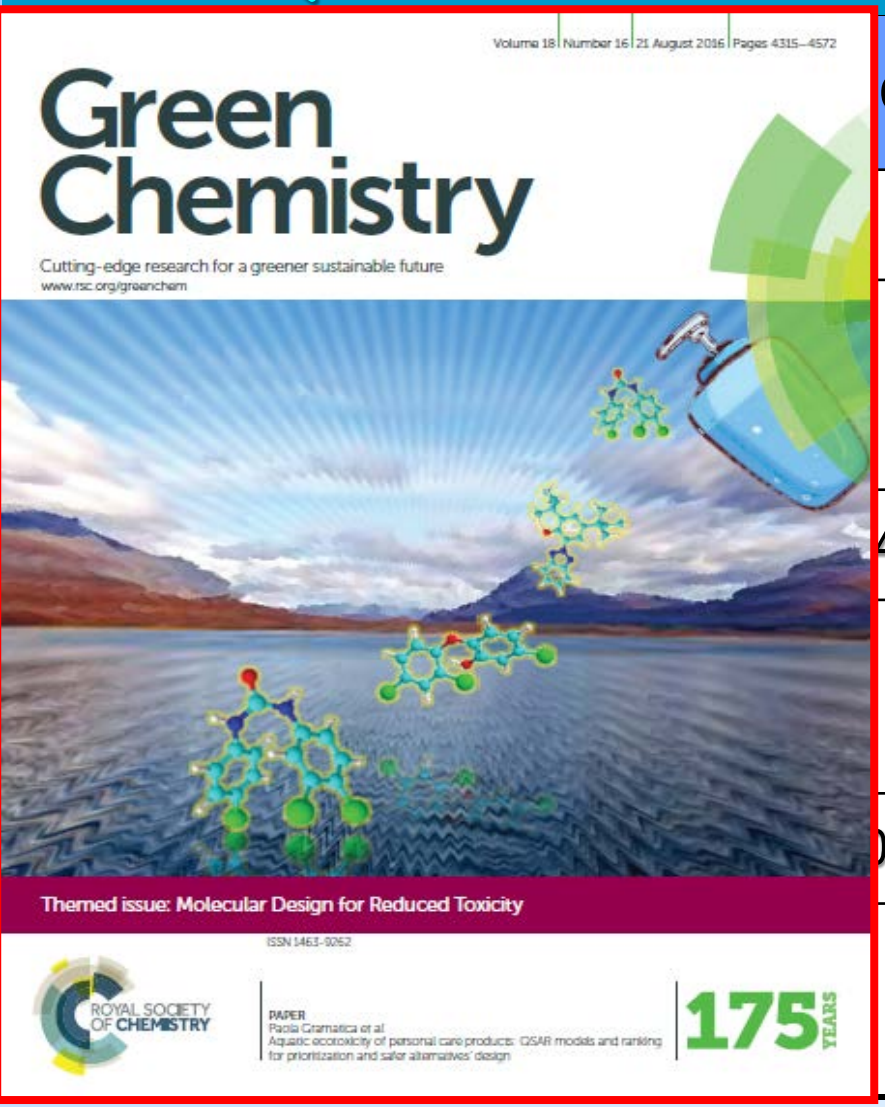
The aquatic toxicity of environmental chemicals is studied by toxicity tests on three different trophic levels: algae, daphnids and fish.

Very limited experimental data availability for PPCPs, mainly of homogeneous data, usefull for QSAR modeling.

Data Curation for homogeneous datasets:

- same species,
- time,
- end point
- etc.

QSAR models for Eco-toxicity of PCPs



Q^2_{LOO}	Q^2_{LMO}	$RMSE_{cv}$	CCC_{ext}	$Q^2_{ext\ Fn}$	%AD
-10.58 + 13.05GGI8 + 21.88Mp					
0.91	0.90	0.45	0.94-0.95	0.87-0.90	98%
49 +0.015MW -3.21ATSC0c – 1.52GATS1p					
0.88	0.87	0.55	0.89-0.95	0.80-0.91	98%
) +0.43XlogP+2.356minHother +15.38AVP-7					
0.79	0.79	0.63	0.85-0.90	0.72-0.86	95%

Externally Predictive Models
High AD to more than
500 PCPs

QSAR models for Eco-toxicity of Pharm.

DATA CURAT

Models' summary		n	R^2	Q^2_{LOO}	Q^2_{LMO}	$RMSE_{cv}$	CCC_{ext}	$Q^2_{ext\ Fn}$	%AD
pEC50 *P. subcapitata*	Eq.	0.93 -3.72minHother -4.61VCH-6 +0.48piPC6 -0.09 VE3_Dt							
	Stat. Par.	45	0.78	0.74	0.73	0.67	0.83-0.88	0.68-0.81	74%
pEC50 *D. magna*	Eq.	0.65 + 0.32 CrippenLogP -0.08 minHBint2-0.06 SpMAD_Dzs – 0.75 AATSC4i + 0.13 C2SP3							
	Stat. Par.	125	0.75	0.72	0.72	0.41	0.84-0.86	0.70-0.79	87%
	Eq.	xHBint2 -1.15HybRatio TSC0v							
		68					0.82-0.86	0.71-0.83	96%
	Eq.	.39nHBAcc+1.11SpMin7_Bhp							
		79					0.87-0.89	0.70-0.86	80%

Environment International xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Hazard of pharmaceuticals for aquatic environment: Prioritization by structural approaches and prediction of ecotoxicity

Alessandro Sangion, Paola Gramatica *

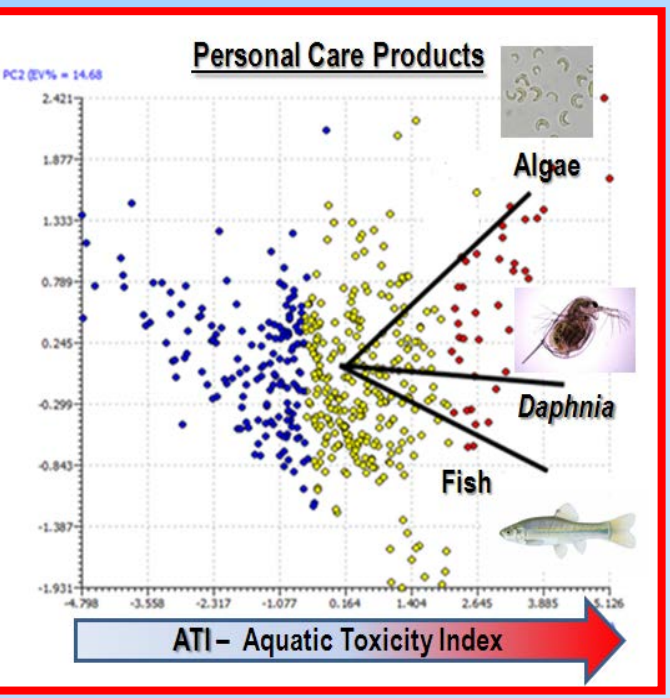
2016, *95*, 131-143

QSAR Research Unit in Environmental Chemistry and Ecotoxicology, Department of Theoretical and Applied Sciences, University of Insubria, Varese, Italy

AD to 1200 Pharm

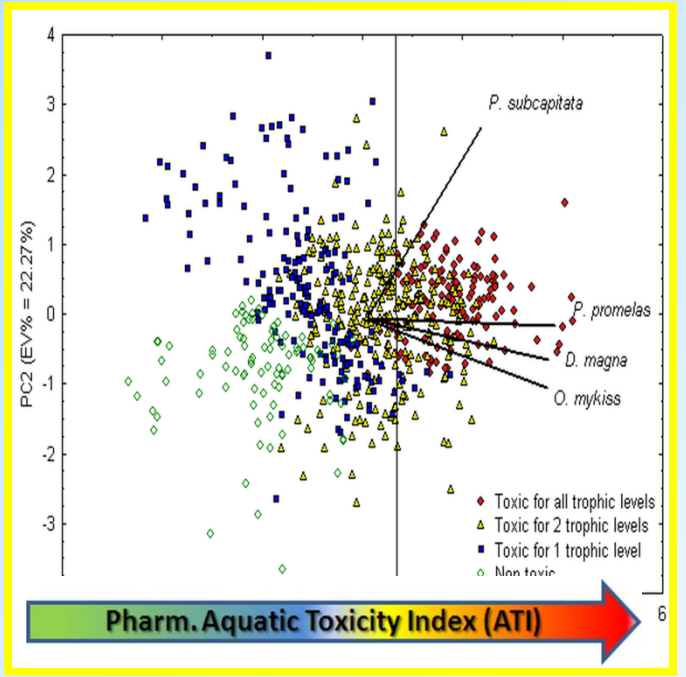
Aquatic toxicity trend of PCPs and Pharm.

Combining toxicities on different organisms: overall aquatic toxicity

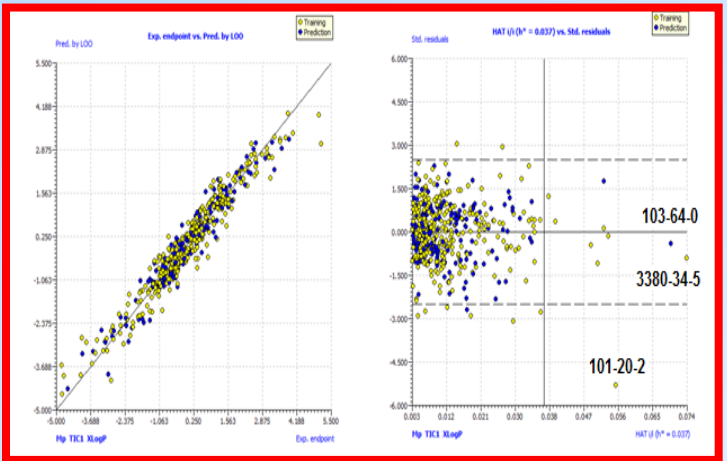


Green Chem., **2016**, *18*, 4315

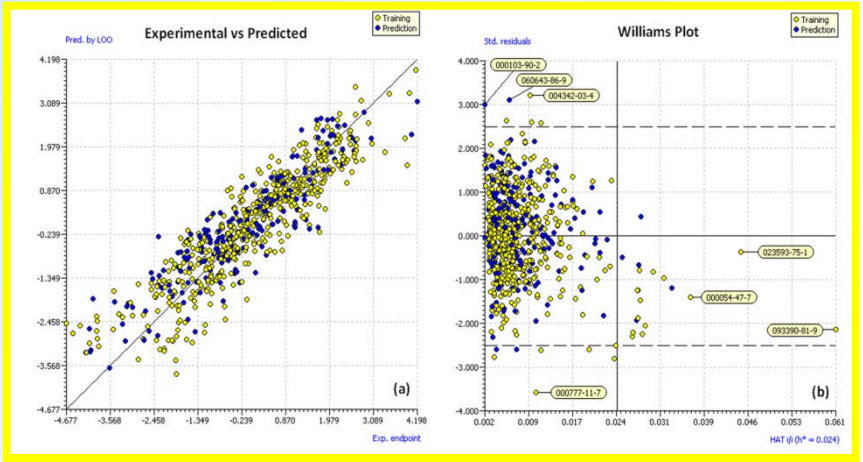
Aquatic Toxicity Index by PCA: ATI



Environ. Int., **2016**, *95*, 131



Plots for QSARs and AD



All the Insubria MLR QSAR models are available and applicable in QSARINS- Chem

http://www.qsar.it

Poster 94 in Environmental Modelling Session

Predictive QSAR models and chemometrics are useful for screening/prioritisation of large sets of chemicals, and for the design of alternative/sustainable chemicals

P. Gramatica. Prioritization of Chemicals Based on Chemoinformatic Analysis, 2016
Handbook of Computational Chemistry Vol 5,
Ed. J. Leszczynski, Springer

Prof. Paola Gramatica - QSAR Research Unit - DiSTA - University of Insubria - Varese (Italy)

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Thanks for your attention !!

http://www.qsar.it

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