QSPR prediction of physico-chemical properties and endocrine disrupting activity of brominated flame retardants

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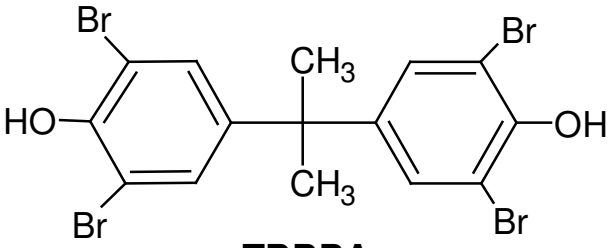
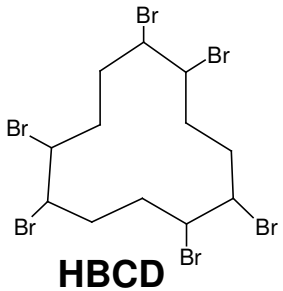
INTRODUCTION

- Class of emerging pollutants used in a variety of consumer products (plastics, polyurethane foams, textiles, electronic equipments..) to increase fire resistancy
- Three most marked HPV products:

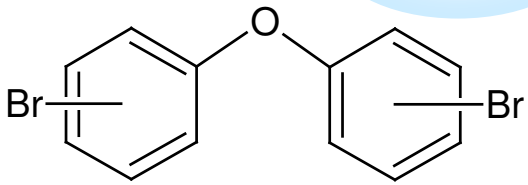
209 possible CONGENERS



TBBPA
TetraBromoBisphenol-A



HBCD
Hexabromocyclododecane



PBDE
Polybrominated Diphenyl Ethers

- Levels in the environment and humans increased since they came into use

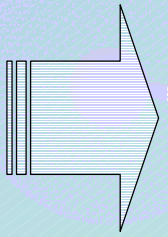
- Ban of penta- and octa-BDE formulations (DecaBDE under evaluation); HBCD in candidate list?

INTRODUCTION

Background knowledge about BFRs:

- Low water solubility
- High LogKow > 5
- Persistence in the environment
- Liver toxicity, thyroid toxicity, developmental toxicity
- Endocrine disruptors

The available amount of experimental data is very small and mainly related to already banned BFRs.



There is the need to extend knowledge about properties and ecotoxicological data for a better understanding of BFRs behaviour and related risks

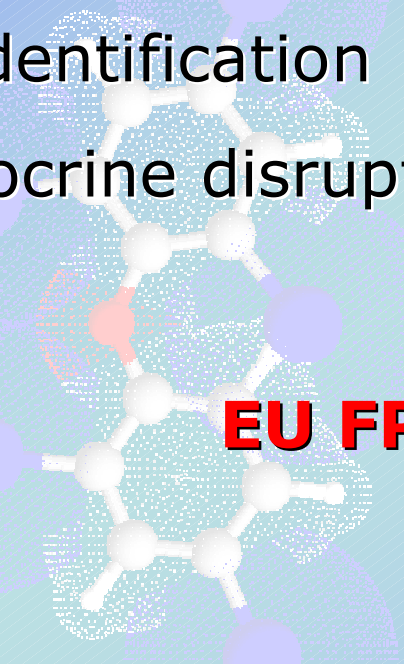
AIMS of the STUDY

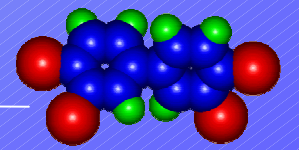
Development of QSAR models for all available endpoints paying attention to external validation and applicability domain analysis

→ Evaluation of environmental behaviour of BFRs

→ Identification of more dangerous compounds for endocrine disruption potency

EU FP7 Project - CADASTER

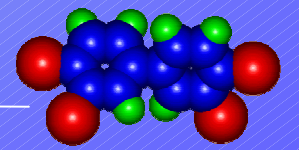




OECD Principles for QSAR models

To facilitate the consideration of a QSAR model for regulatory purposes, it should be associated with the following information:

- a defined endpoint
- an unambiguous algorithm
- a defined domain of applicability
- appropriate measures of goodness of fit, robustness and predictivity
- a mechanistic interpretation, if possible



Application of the OECD principles for QSAR models

1. Defined end-points of Phys-chem and Endocrine Disruption
2. Unambiguous algorithm.

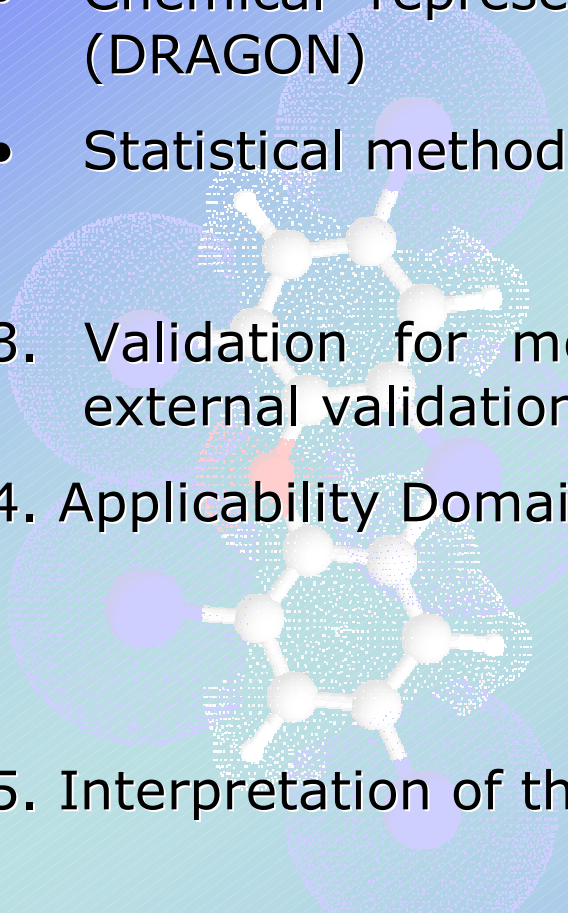
- Chemical representation by theoretical molecular descriptors (DRAGON)
- Statistical methods → MLR regression (OLS)

  → Classification methods (K-NN)

3. Validation for model stability and predictivity (internal and external validation)
4. Applicability Domain Analysis:

   → leverage approach (MLR)

   → descriptors space (Classification)
5. Interpretation of the selected molecular descriptors, if possible.



RESULTS – *QSAR models*

Physico-chemical and degradation Properties

Endpoint	Model	Train obj.	Test obj.	Desc.	R^2%	Q^2_{LOO} %	Q^2_{EXT} %	AD% on 220 BFR
$LogK_{OA}$	Full	30		*T(O..Br)*	97.4	96.8	-	90.4
	k-ANN Split	24	6		96.1	95.0	95.2	-
$LogK_{OW}$	Full	20		*T(O..Br)*	96.4	95.6	-	93.6
	k-ANN Split	14	6		97.1	95.9	94.7	
MP	Full	25		*X2A*	84.4	81.9	-	98.6
	k-ANN Split	20	5		82.2	78.5	93.7	-
$LogP_L$	Full	34		*T(O..Br)*	98.7	98.5	-	91.4
	k-ANN Split	28	6		98.8	98.5	98.6	-
LogS	Full	12		*Mor23m*	91.8	88.6	-	96.8
LogH	Full	7		*BEHe7*	96.9	93.3	-	61.4
LogKp*	Full	15		*MW*	94.9	93.8	-	91.0
LogHLp*	Full	15		*T(O..Br)*	94.4	92.7	-	83.9

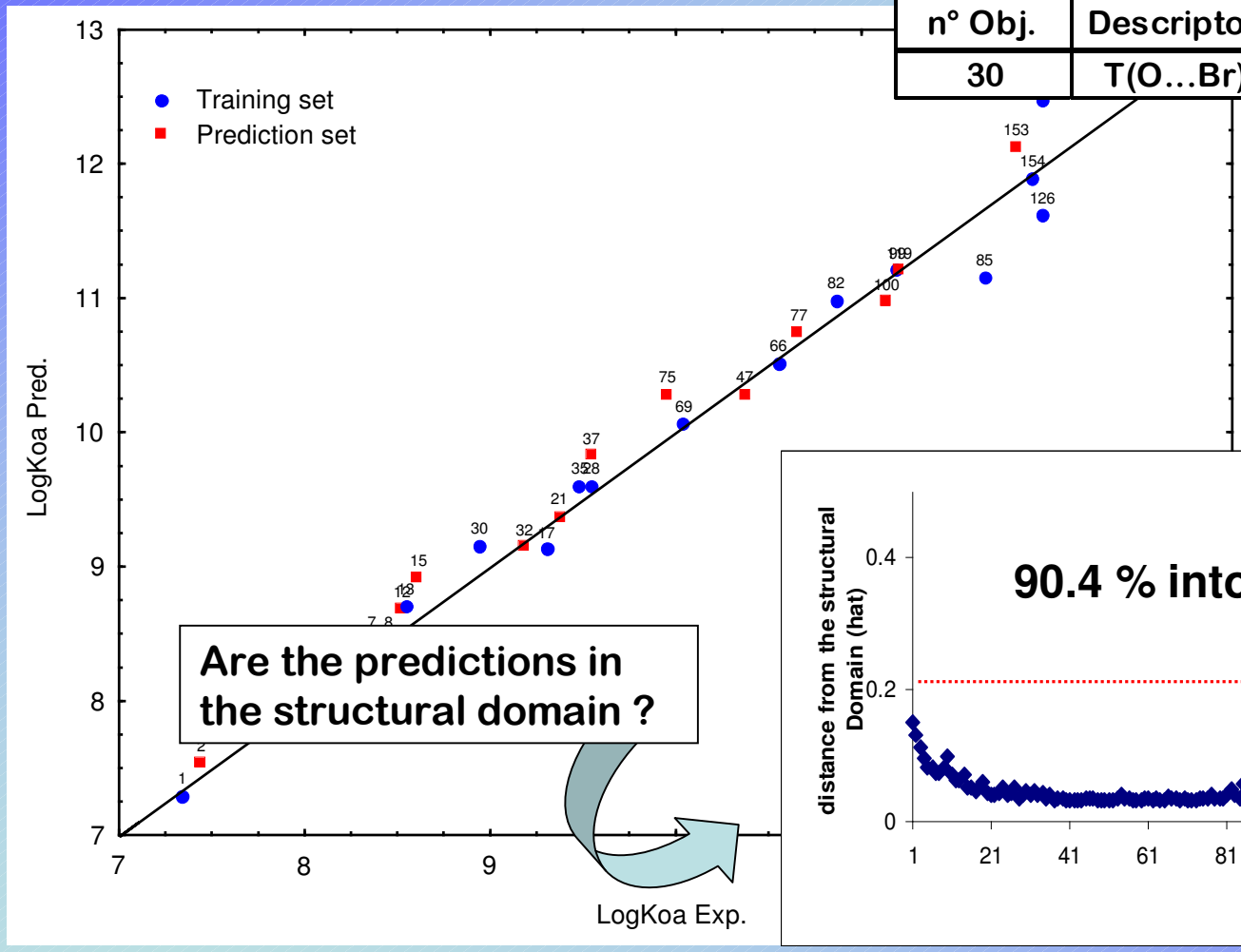
** Photodegradation*

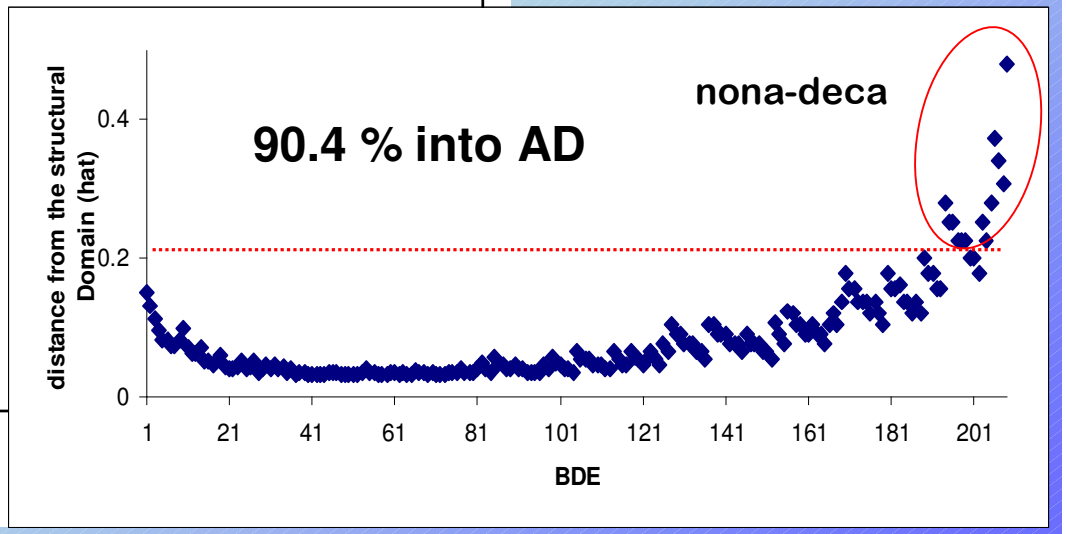
E. Papa, S. Kovarich, P. Gramatica, 2009. *Development, validation and inspection of the applicability domain of QSPR models for physico-chemical properties of polybrominated diphenyl ethers.* QSAR & Comb. Sci., *28*, 790-796.

Model for Log Koa

LogKoa= 6.658 +0.222 T(O…Br)

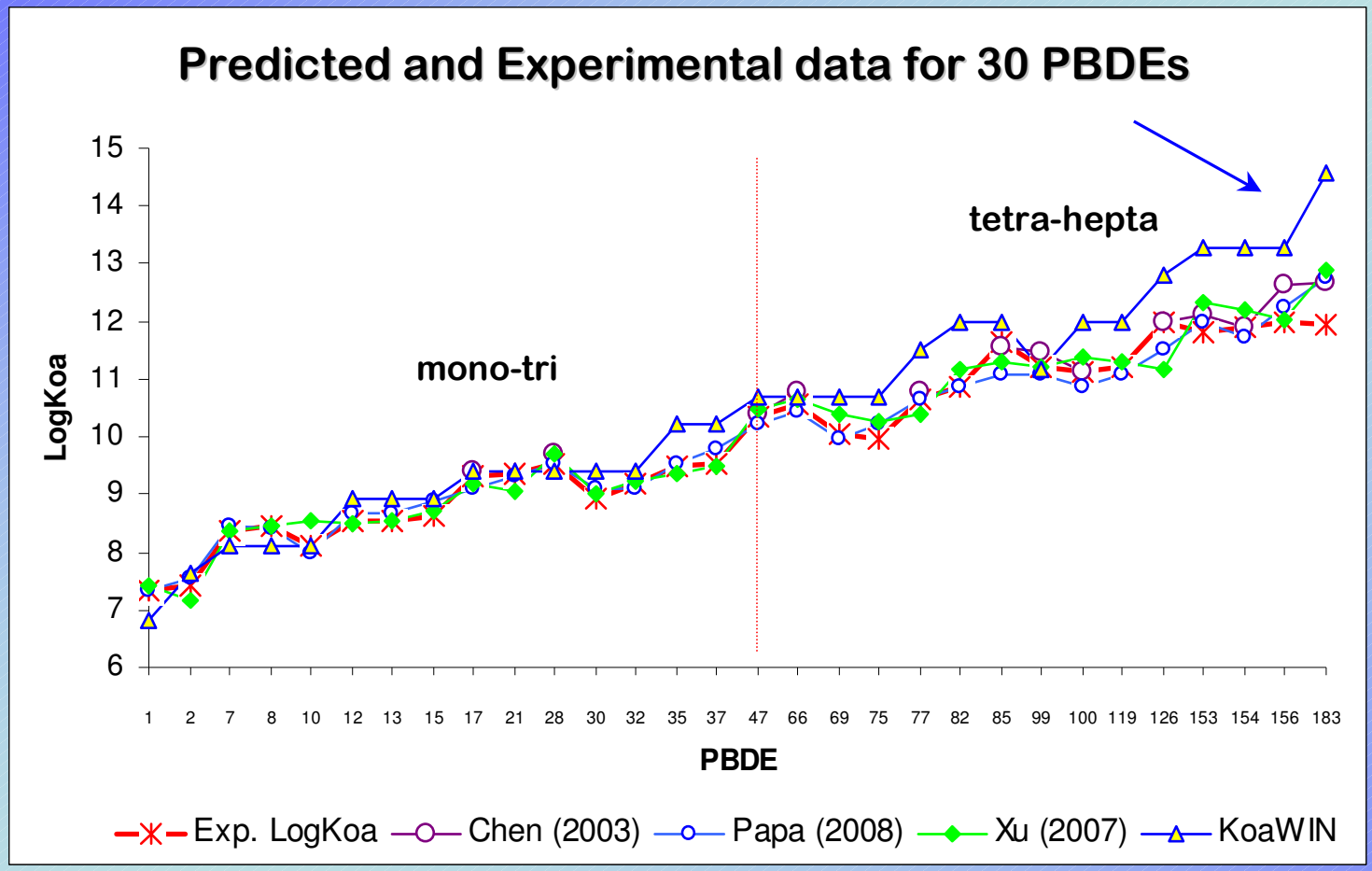
n° Obj.	Descriptor	R^2%	Q^2%	$Q^2_{EXT\ (rand50\%)}$%
30	T(O…Br)	97.37	96.78	95.17





Experimental range of LogKoa: 7.34 (mono-BDE) – 11.96 (hepta-BDE)

Comparison with existing models

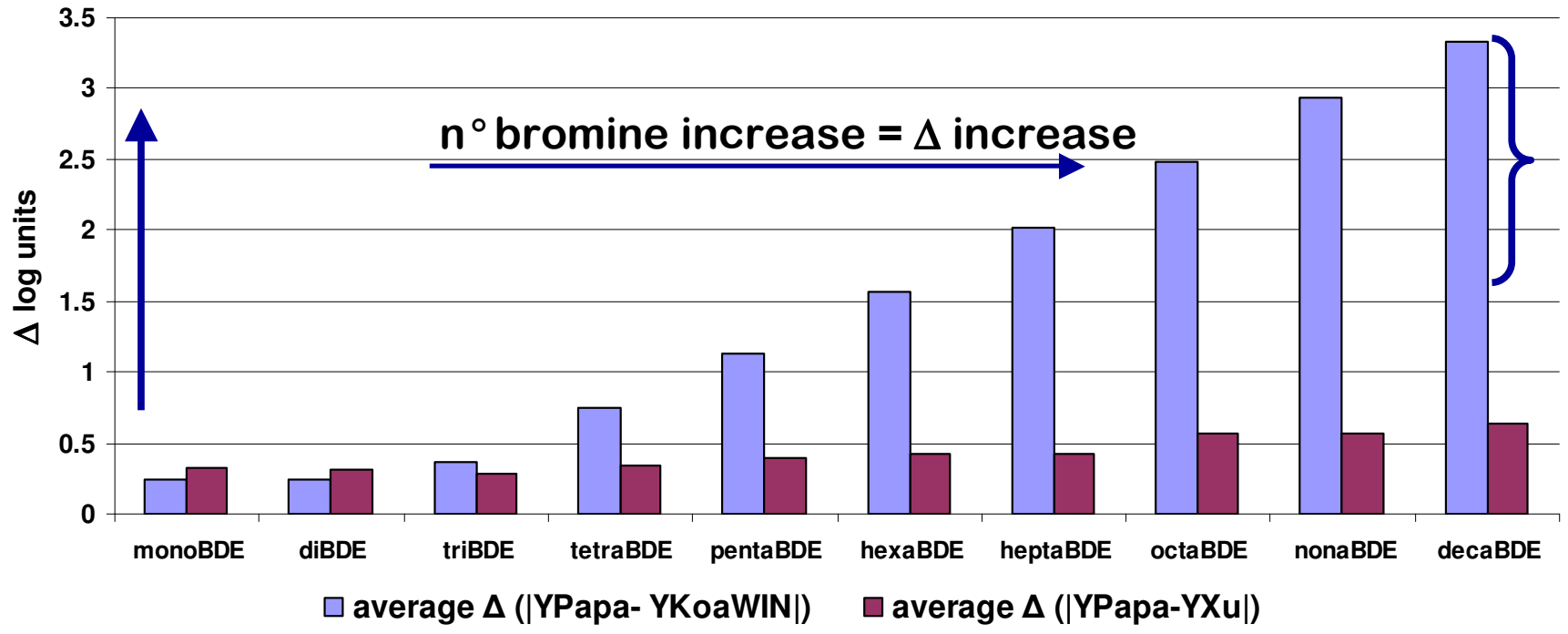


Author	Method	n° obj.	n° vars	R^2%	Q^2%	Q^2_{EXT}% (rand50%)	RMSE (30 obj.)
Papa et al. (2009)	MLR	30	1	97,37	96,68	95,17	0,25
Xu et al. (2007)	MLR	22	2	97,61	97,25	-	0,31
Chen et al. (2003)	PLS	13	10	98,13	97,59	-	-

	RMSE $_{25obj}$
KoaWIN	0,47
Papa et al. (2009)	0,23
Xu et al. (2008)	0,21

Comparison with existing models

Predictions for 209 PBDEs



Y_{Papa} = Predictions by our model (range Log Koa: 7.32 – 15.09)
$Y_{Episuite}$ = Predictions by KoaWIN (Δmax = 3.33 log units; range Log Koa: 6.81-18.23)
Y_{Xu} = Predictions by Xu et al. (2007) (Δmax =1.06 log units; range Log Koa: 7.4-15.73)

RESULTS – Interpretation of descriptors

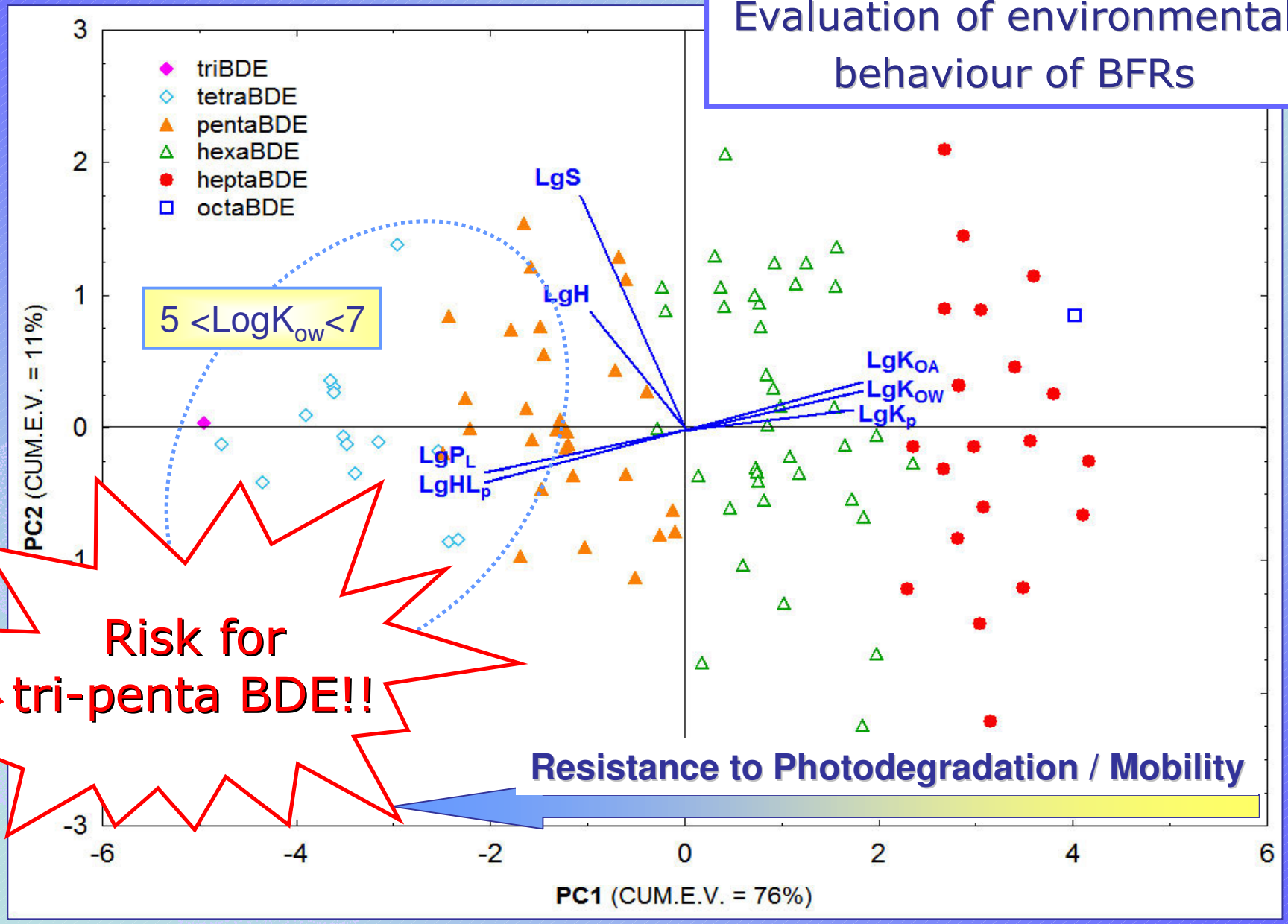
The same descriptor, i.e. **T(O…Br),** was selected as the best modeling variable for three different properties which are related to each other (**$LogP_L$, LogKoa, LogKow, $LogHL_p$**).

This descriptor gives a double structural information: its values increases according to both the **number** and the **distance of bromine substituents** from the oxygen ether, on each phenyl ring.

Thus, **T(O…Br)** takes also into account the information related to the **position of the bromine atoms on the phenyl rings.**

RESULTS - *Physico-chemical and degradation Properties*

Evaluation of environmental behaviour of BFRs



Risk for tri-penta BDE!!

Resistance to Photodegradation / Mobility

RESULTS – *QSAR models of Endocrine Disrupting Potency*

DATA SETS

END-POINT		N° EXP DATA	SOURCE
T4-TTR comp	T4-TTR Competition Potency	29	Hamers *et al.* (2006,2008)
E2SULT inh	E2SULT Inhibition Potency	29	Hamers *et al.* (2006,2008)

Classification Models (k-NN Method)

EXTERNAL VALIDATION * on split data

* **P. Gramatica, Principles of QSAR models validation: internal and external *QSAR Comb.Sci.* 2007, 26(5), 694-701**

Classification criteria according to Hamers et al. (2006)

CRITERIA	POTENCY
Response < 20% of control	no potency
IC_{50} > 10 µM & resp > 20% of control	low potency
1.0 µM < IC_{50} < 10 µM	moderate potency
0.1 µM < IC_{50} < 1.0 µM	high potency
0.01 µM < IC_{50} < 0.1 µM	very high potency

CLASSES

1 **NO POTENCY**

2 **LOW/MODERATE POTENCY**

3 **(VERY) HIGH POTENCY**

RESULTS – *Endocrine Disruptor Potency*

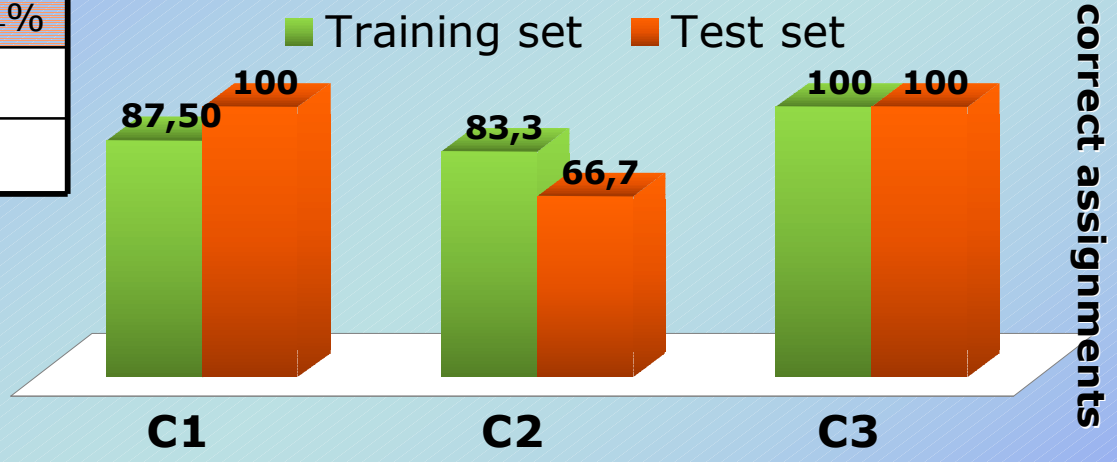
T4-TTR Competition

Model	K	n_{TR}	n_P	NER%	NER_{EXT}%
Full	3	29	-	93.1	-
Split	3	19	10	89.5	90

DISPv qpmax

Geometrical descriptor

Charge descriptor



E2SULT Inhibition

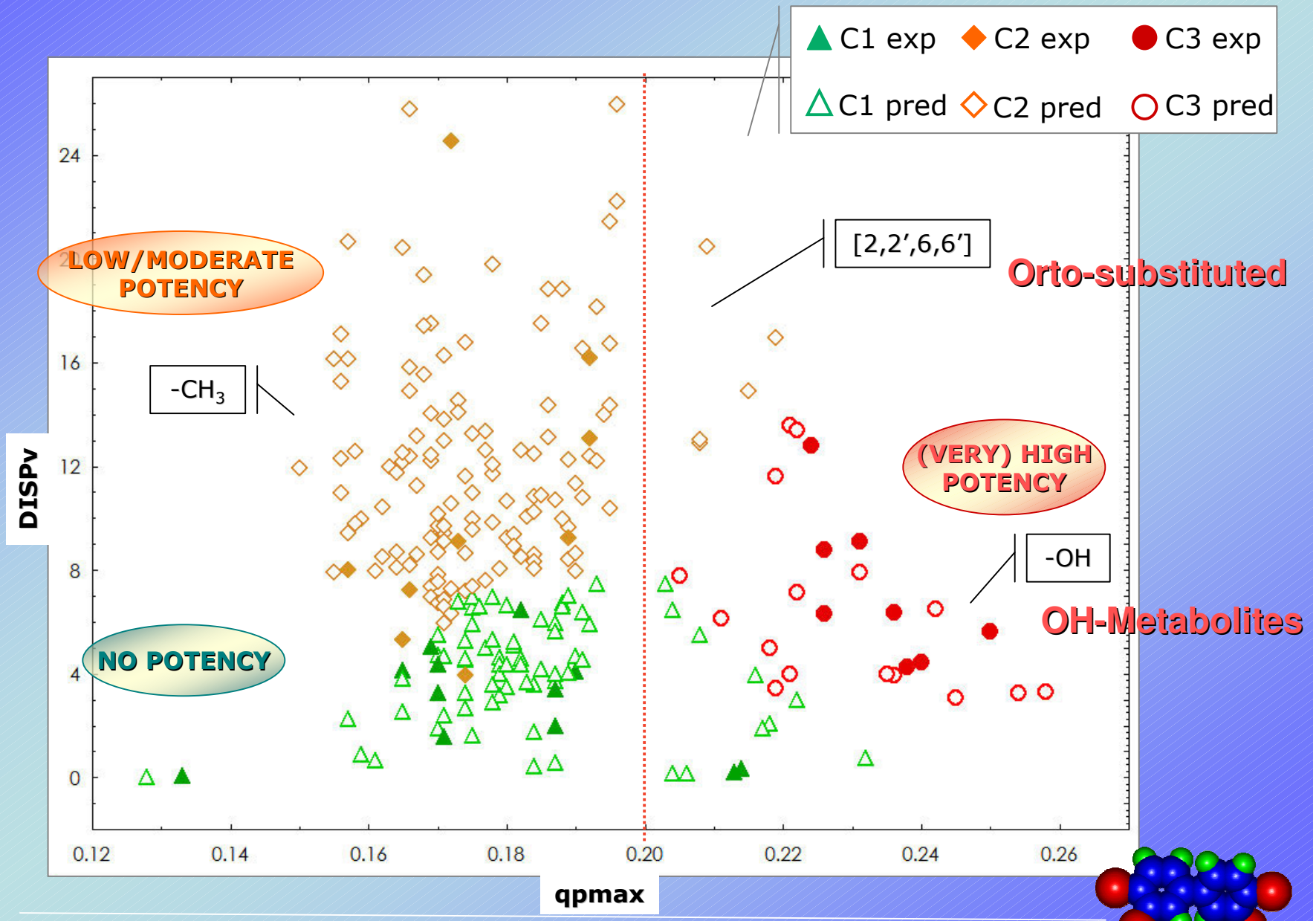
Model	K	n_{TR}	n_P	NER%	NER_{EXT}%
Full	1	29	-	89.6	-
Split	1	21	8	76.2	100

HATSv F08[Br-Br]

GETAWAY descriptor

2D Frequency Fingerprint

Applicability domain T4-TTR



Conclusions

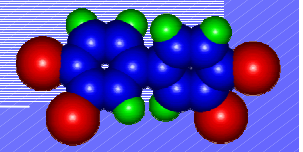
- **Predictive models were developed *ad-hoc* for several physico-chemical properties, degradation parameters and endocrine disrupting potency of BFR, according to the OECD principles for QSAR.**

  → simplicity (few descriptors)

  → external validation

  → AD analysis for more then 200 BFRs

- **Our QSARs could be used to fill data gaps according to the new REACH regulation, they can facilitate the screening and prioritization of chemicals as well as to help the search for alternative/safer chemicals**



Financial support from FP7-EU CADASTER Project

THANK YOU for your attention!

http://www.qsar.it

Physico-chemical and degradation Properties

DATA SETS

END-POINT	N° EXP DATA	SOURCE
H Henry's Law Const. [Pa m^3/mol, 25°C]	7	Cetin and Odabasi (2005)
T_M Melting Point [°C]	25	Marsh *et al.* (1999); Tittlemier *et al.* (2002); Palm *et al.* (2002); Kuramochi *et al.* (2007)
P_L Vapour Pressure [Pa, 25°C]	34	Wong *et al.* (2001); Palm *et al.* (2002); Wania and Dugani (2003)
S Water Solubility [mol/L, 25°C]	12	Tittlemier *et al.* (2002)
LogKoa Octanol-Air Partition Coef.	30	Harner and Shoeib (2002); Wania *et al.* (2002); Gouin and Harner (2003)
LogKow Octanol-Water Partition Coef.	20	Palm *et al.* (2002); Wania and Dugani (2003) Braekevelt *et al.* (2003);Kuramochi *et al.* (2007)
K_pPhotodegradation Rate	15	Eriksson *et al.* (2004)
HL_pPhotodegradation Half-Life	15	Eriksson *et al.* (2004)