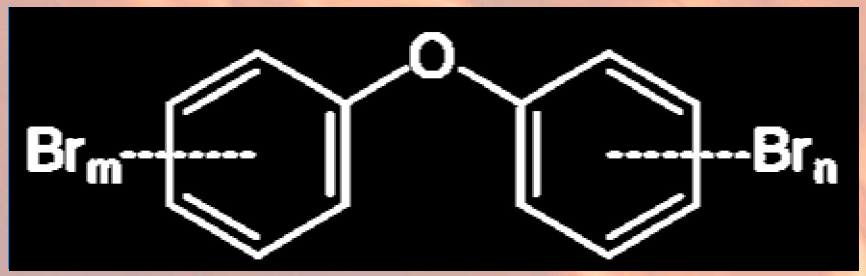
QSPR prediction of physico-chemical properties and degradation of PBDEs

Ester Papa, Simona Kovarich, and Paola Gramatica
QSAR Research Unit in environmental chemistry and ecotoxicology
DBSF -University of Insubria, Varese - Italy

e-mail: paola.gramatica@uninsubria.it
ester.papa@uninsubria.it

INTRODUCTION – why PBDEs?



Polybrominated Diphenyl Ethers
209 congeners

- Class of brominated flame retardants added to plastics, polyurethane foams, textiles, electronic equipmemts..
- Have been marketed in 3 formulations:

  “penta”, “octa”, “deca” – different % of congeners
- Levels in the environment and humans increased since they came into use
- Ban of “penta” and “octa” formulations since 2004

INTRODUCTION – why PBDEs?

Background knowledge about PBDEs:

- Low water solubility < 1 μg/kg
- High LogKow > 5
- Instability of the highly brominated congeners
- Persistence of medium brominated congeners
- Liver toxicity, thyroid toxicity, developmental toxicity
- Most of the data are available for a few congeners only (i.e. 28, 47, 99, 100, 138, 153, 154,183, 209); insufficient data is available for the other PBDEs

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

This topic is included in the FP7- EU Project CADASTER under negotiation.

AIMS of the STUDY

- Overview of the data for physico-chemical properties of PBDEs available in literature, and compilation of the experimental data set.
- Development of QSPR models (linear regression) for all available endpoints with strong external validation.
- To compare our results with other existing QSPR models.

Materials and Methods

1 - Dataset	n° of available exp.data (→modelled)	Bibliography	Comparison with other *ad hoc* models
Henry Low Constant (H) (Pa m3/mol, 25°C)	12 → 7	Cetin & Odabasi (2005) Tittlemeier et al. (2002)	Xu et al. (2007)
Melting Point (MP °C)	26	Kuramochi et al. (2007) Tittlemeier et al. (2002) Palm et al. (2002) Marsh et al. (1999)	not available
Vapour Pressure (P_L) (Pa, 25°C)	39 → 35	Wania & Dungani (2003) Tittlemeier et al. (2002) Palm et al. (2002) Wong et al. (2001)	Xu et al. (2007)
Water Solubility (S) (mol/L, 25°C)	13 → 12	Kuramochi et al. (2007) Wania & Dungani (2003) Tittlemeier et al. (2002) Palm et al. (2002)	not available
Log Koa	30	Gouin and Harner (2003) Harner & Shoeib (2002) Wania et al. (2002)	Xu et al. (2007) Chen et al. (2003)
Log Kow	20	Kuramochi et al. (2007) Wania & Dungani (2003) Braekevelt et al. (2003) Palm et al. (2002)	not available
Logk $_{photol.}$	15	Eriksson et al. (2004)	Niu et al. (2006) Chen et al.
Half life $_{photol.}$	15	Eriksson et al. (2004)	not available
Logk $_{hydrol.}$	7	Rahm et al. (2005)	not available
Half life $_{hydrol.}$	7	Rahm et al. (2005)	not available

Materials and Methods

2 – Theoretical Molecular Descriptors

- Over 1600 mono-, bi- and tri-dimensional theoretical molecular descriptors were calculated for the studied compounds using DRAGON
- Constant and near to constant variables were eliminated
- To check for and eliminate pair correlations
- Four quantum-chemical descriptors were calculated using Hyperchem-MOPAC.
- The final number of variables used to build the QSPR models was 620

Materials and Methods

3 – QSPR – Modelling and validation

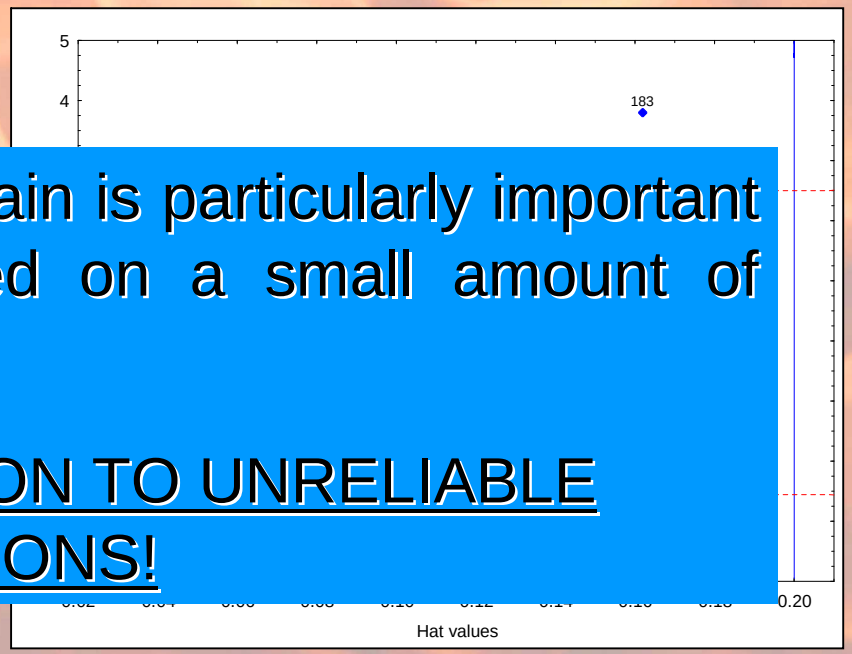
- Linear Regression QSPRs developed for all the endpoints (models including 1 or 2 variables – All Subset variable selection method).
- Internal validation: to verify the robustness of the model based on the training set only.
- External validation: to verify the real predictivity of the models using chemicals that are not included for the development of the model (training set).

External validation was performed by splitting the data into training and prediction sets using the Random by Response method (50% as prediction set).

Materials and Methods

4 – QSPR – Applicability Domain (verified for 209 PBDEs)

- The approach based on the leverage distance was applied for the analysis of the structural domain of the models (check for unreliable predictions).
- Standardised residuals were calculated to identify outliers for the response (residuals > 2.5σ).
- Williams Plot



To check the Applicability Domain is particularly important since these models are based on a small amount of experimental data:

RISK OF EXTRAPOLATION TO UNRELIABLE PREDICTIONS!

RESULTS

Endpoint	Obj. training	Descriptors	R^2%	Q^2%	Q^2_{EXT} % (rand50%-30%*)	AD% (209 PBDEs)
logH	7	BEHe7	96.87	93.34	90.84*	64.7
MP	26	X2A	84.56	82.24	88.55	97.61
$\log P_L$	34	T(O…Br)	98.63	98.45	98.62	91.38
logS	12	Mor23m	91.8	88.55	85.04	95.69
LogKoa	30	T(O…Br)	97.37	96.78	95.17	92.34
LogKow	20	T(O…Br)	96.44	95.63	91.6	96.65
$\log k_{photol.}$	15	MW	94.91	93.83	92.93	92.82
$\log k_{hydrol.}$	7	HATS2p	91.19	85.05	98.8*	73.68
$\text{Half-Life}_{photol.}$	15	T(O…Br)	94.39	92.66	90.97	86.6
$\text{Half-Life}_{hydrol.}$	7	PW3	96.22	92.07	97.15*	88.99

Focus on the following aspects of interest:

VALIDATION

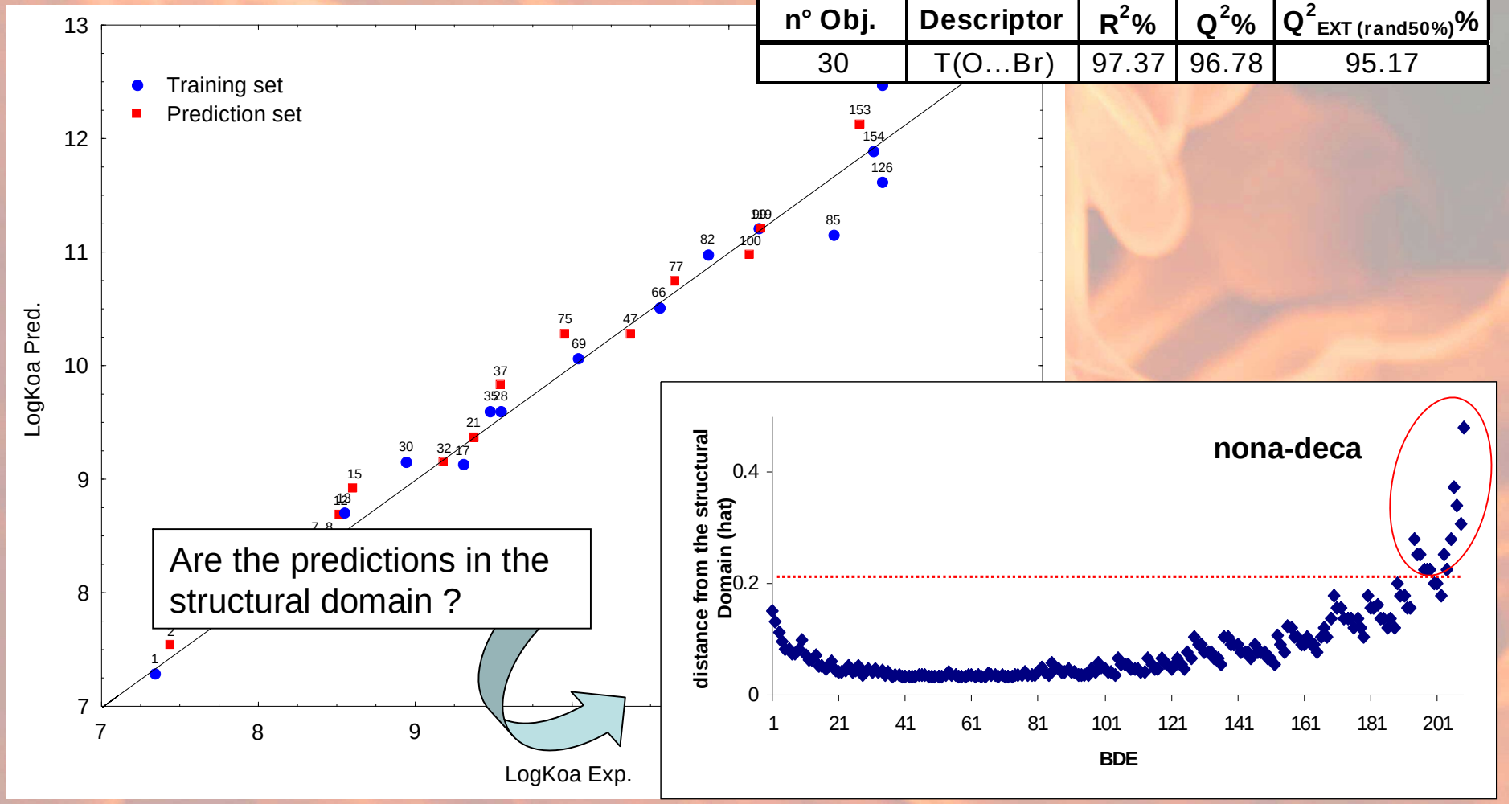
DOMAIN

COMPARISON

Model for Log Koa

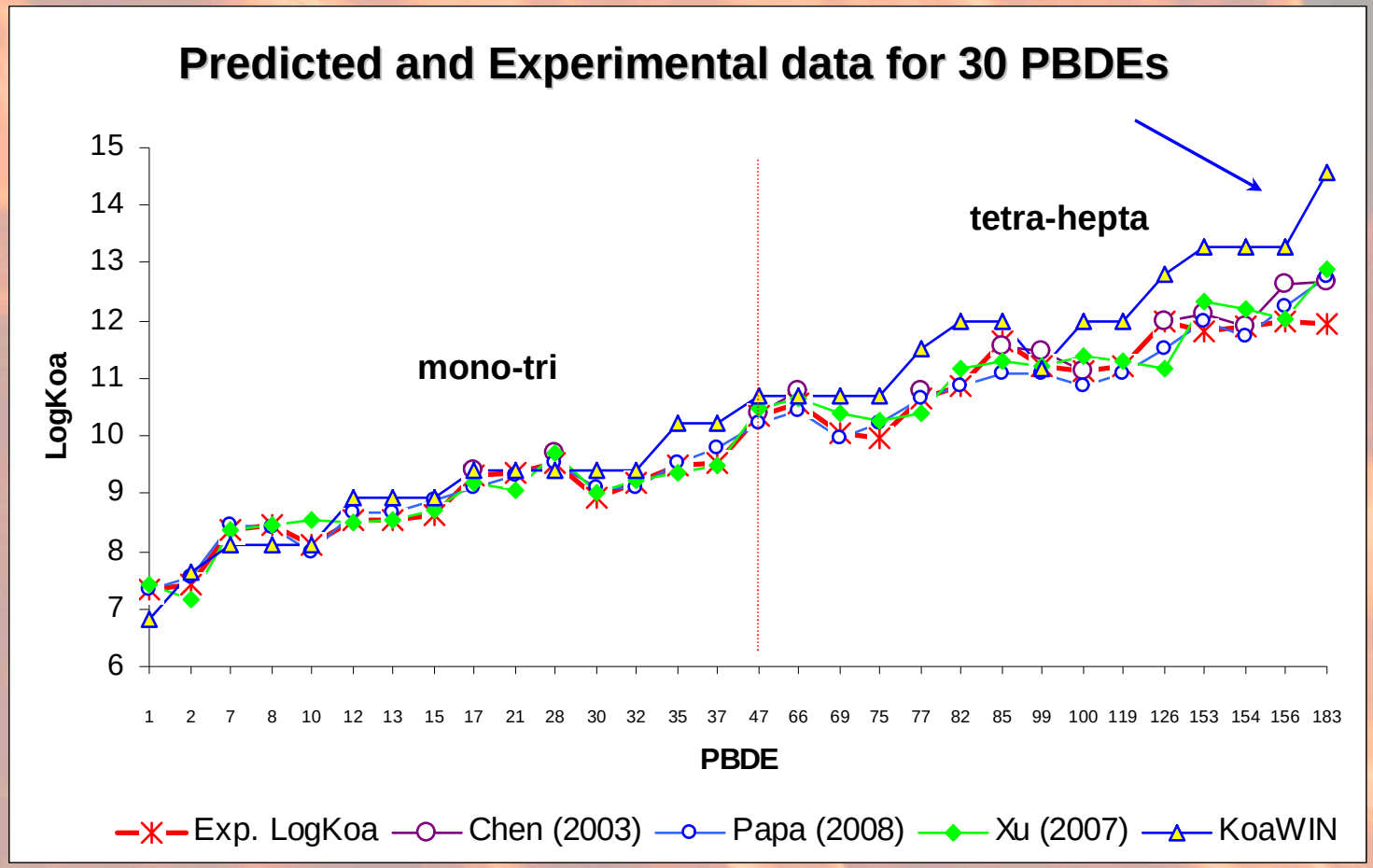
LogKoa= 6.658 +0.222 T(O...Br)

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

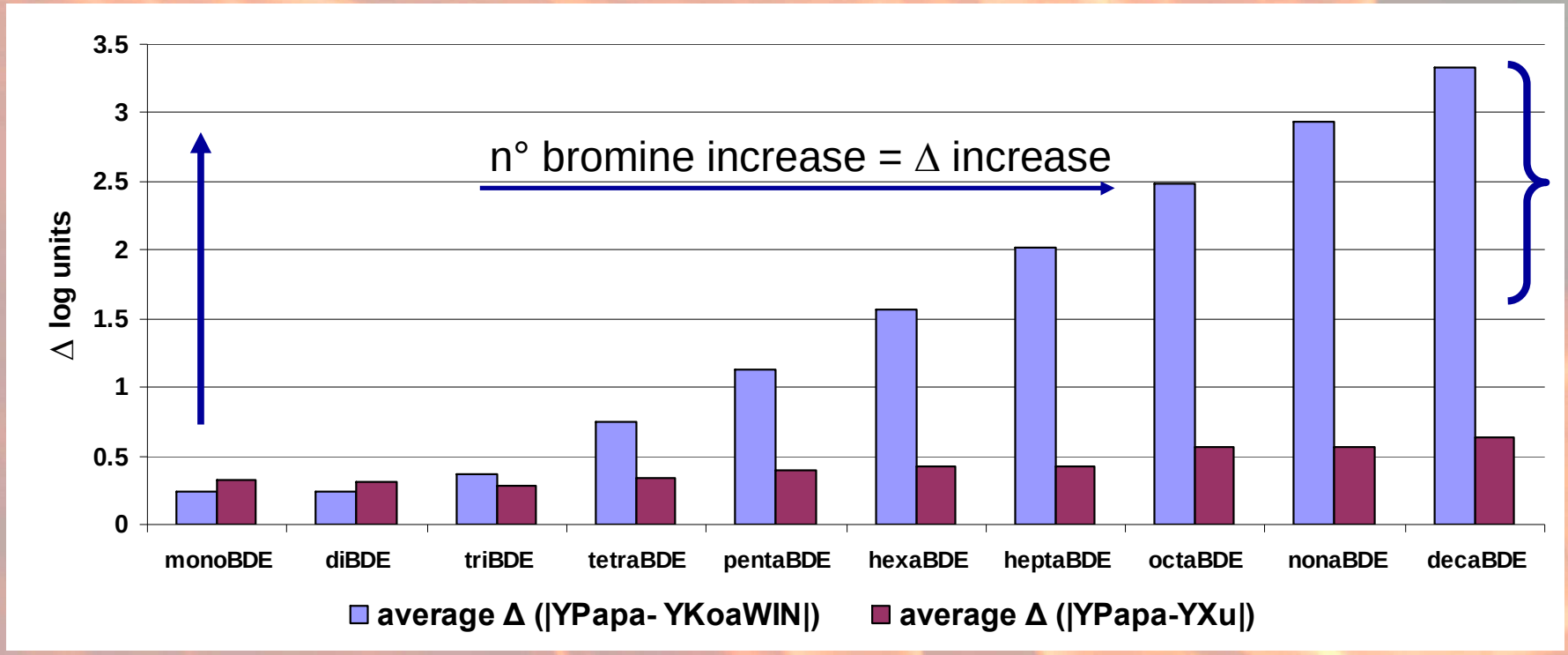


Author	Method	n° obj.	n° vars	R^2%	Q^2%	Q^2_{EXT}% (rand50%)	RMSE (30 obj.)
Papa et al. (2008)	**MLR**	**30**	1	97.37	96.68	95.17	0.25
Xu et al. (2007)	**MLR**	**22**	2	97.61	97.25	-	0.31
Chen et al. (2003)	**PLS**	**13**	10	98.13	97.59	-	-

	RMSE $_{25obj}$
KoaWIN	0.47
Papa et al. (2008)	0.23
Xu et al. (2008)	0.21

Comparison with existing models

Predictions for 209 PBDEs

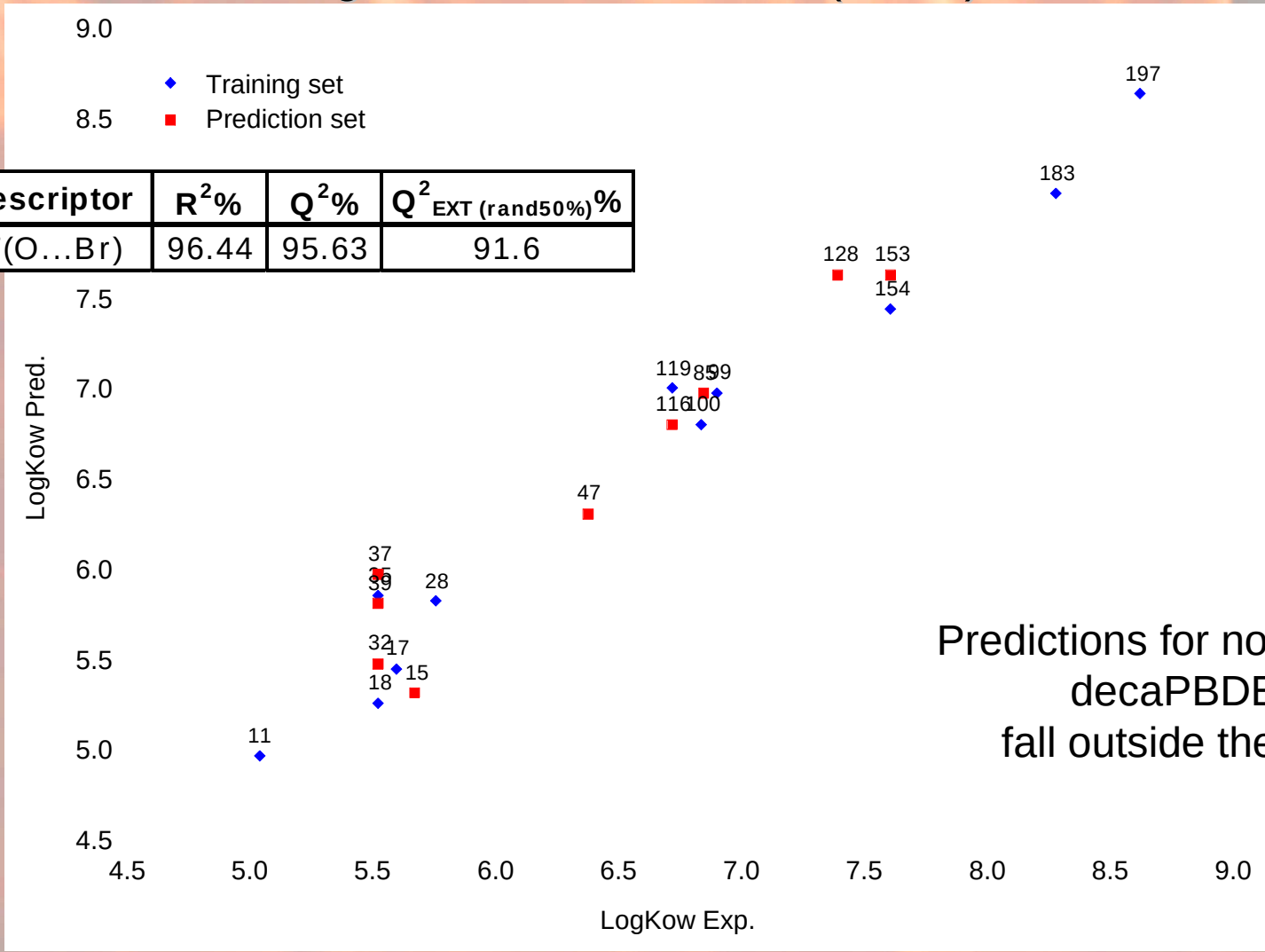


Y_{Papa} = Predictions by our model (range Log Koa: 7.32 – 15.09)
$Y_{Episuite}$ = Predictions by KoaWIN (Δmax = 3.33 log units; range Log Koa: 6.81-18.23)
Y_{Xu} = Predictions by Xu et al. (2007) (Δmax =1.06 log units; range Log Koa: 7.4-15.73)

Model for Log Kow

LogKow= 3.675 + 0.162 T(O...Br)

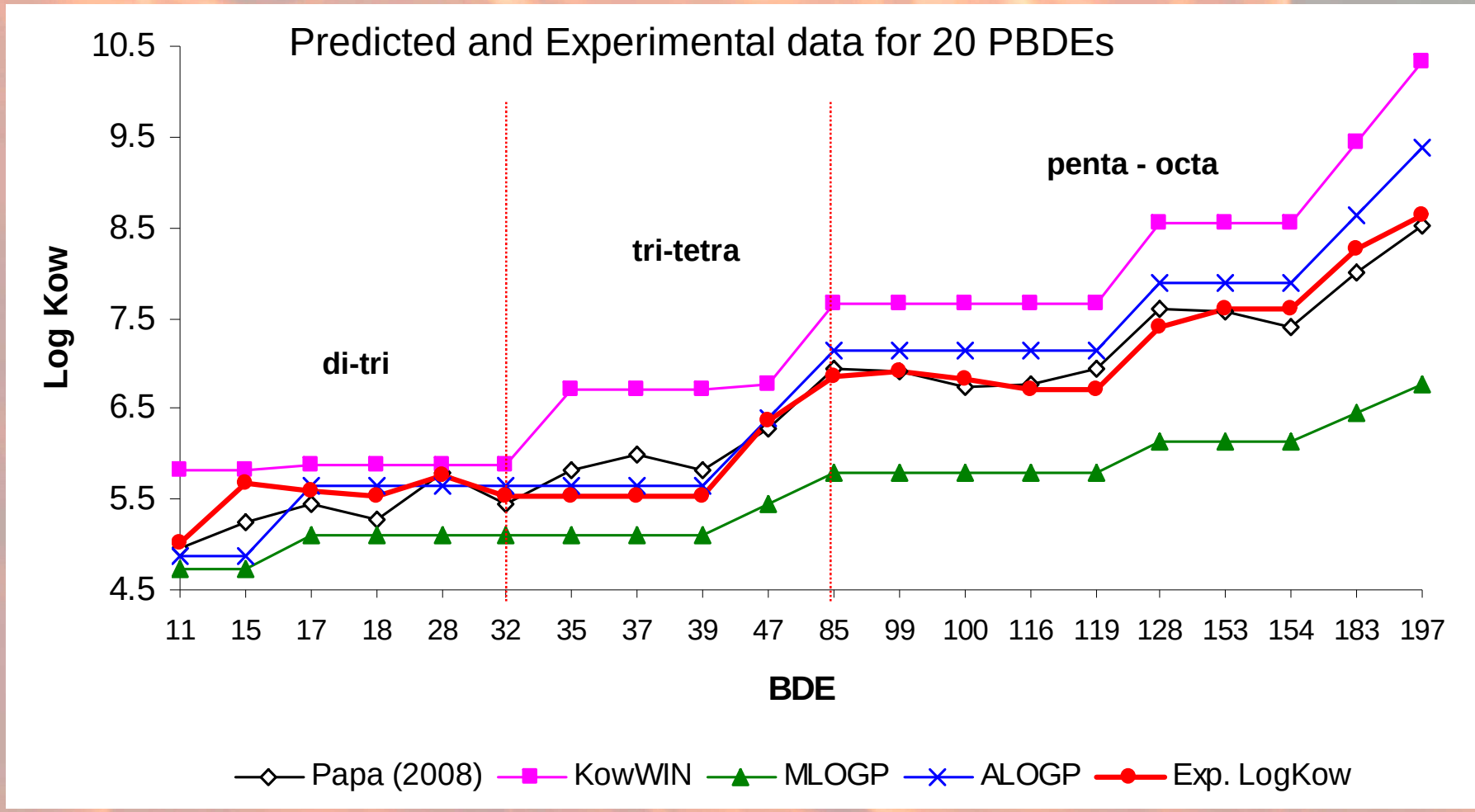
n° Obj.	Descriptor	R^2%	Q^2%	$Q^2_{EXT\ (rand50\%)}$%
20	T(O...Br)	96.44	95.63	91.6



Predictions for nona- and decaPBDE fall outside the AD

Experimental range of LogKow: 5.03 (di-BDE) – 8.62 (octa-BDE)

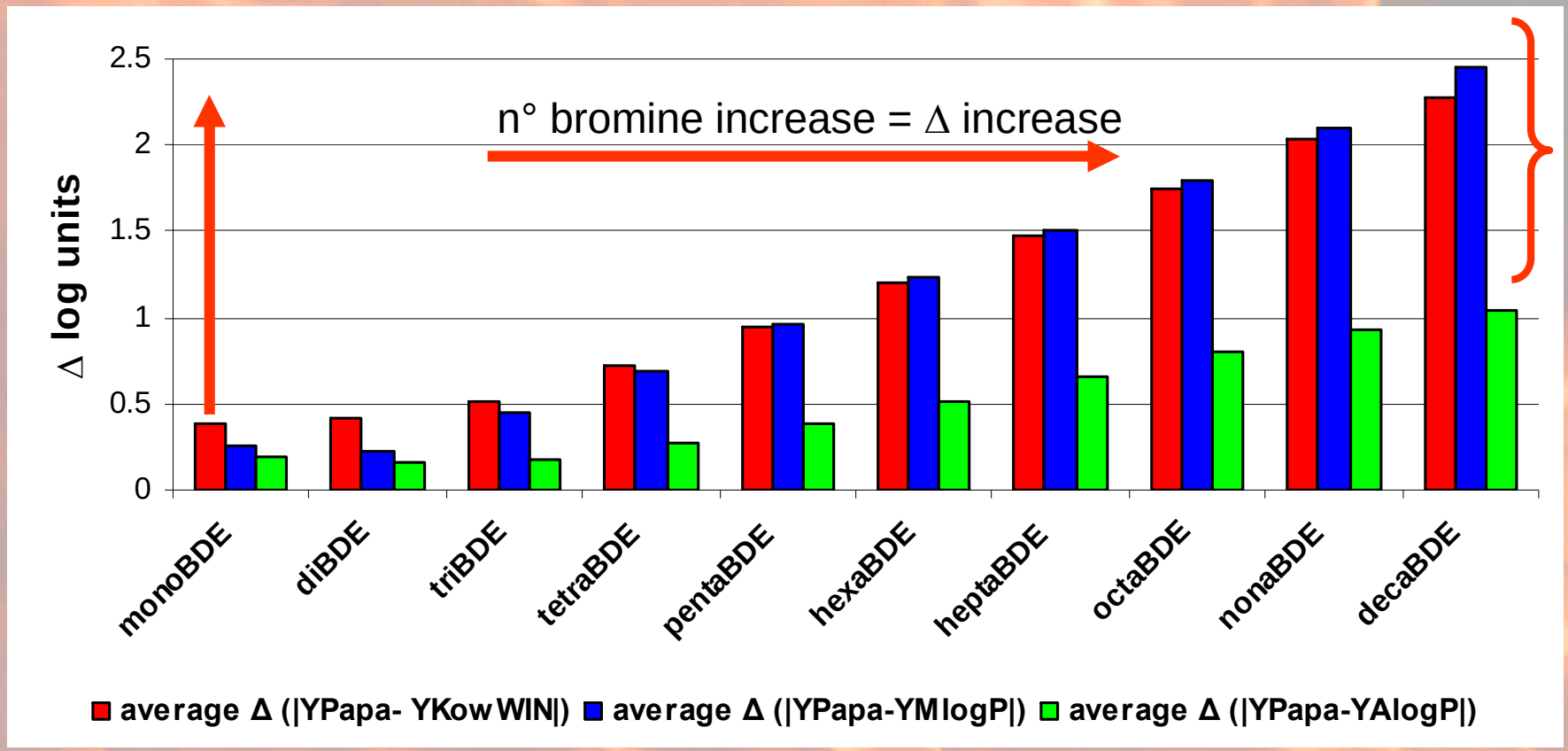
Comparison with existing models



Experimental range of LogKow: 5.03 (di-BDE) – 8.62 (octa-BDE)

Comparison with existing models

Predictions for 209 PBDEs



Y_{Papa} = Pred. by our model (range of LogKow: 4.2 – 9.8)
Y_{Kowwin} = Pred. by KowWIN (Δmax = 2.27 log units; range of LogKow: 4.1 – 12.1)
Y_{MlogP} = Pred. by MLogP (Δmax =2.45 log units; range of LogKow: 4.1-7.4)
Y_{AlogP} = Pred. by ALogP (Δmax = 1.15 log units; range of LogKow: 4.1 –10.9)

Conclusions (1)

- New predictive models were developed *ad-hoc* for several physico-chemical properties and degradation parameters of the 209 PBDE congeners, according to the OECD principles for QSAR.

  ⇒LogKow, MP, Water Solubility, Half-life$_{photo}$, Half-life$_{hydro}$: modeled for the first time for PBDEs (no comparison in literature).

  ⇒LogKoa, Henry Law constant, P_L, k_{photo} : our statistical results are equal to, or better than, those of the existing *ad hoc* models.

- Advantages of our models: simplicity (1 descriptor only), strong external validation provided, AD is determined for all the 209 PBDE congeners.

- The accuracy of *ad hoc* models is higher than "non specific" models (i.e. KoaWIN, KowWIN, MlogP, AlogP).

Conclusions (2)

- Check AD! ~ 90% of the predictions from our models fell into their AD (reliable predictions).

  Exceptions are: models developed for LogH and for $Logk_{hydrol}$ (covered domain respectively: 65% and 73%; mono, di and tri PBDEs outside the AD - unreliable predictions)

- There is a need for more experimental data :

1) to increase the AD for our models.
2) to define a clearer mechanistic interpretation of these QSPRs, by clarifying the relationships among the Br position and the properties/reactivities. (See also POSTER POP24175E).

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

(coming soon CADASTER EU Project - FP7)


THANK YOU!