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

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INTRODUCTION

Brominated flame retardants (BFRs), are an emerging group of persistent organic pollutants, widely used in a variety of consumer products, which activity as endocrine disruptors (EDs) has already been experimentally demonstrated for some congeners. At present, only a small amount of experimental data are available for biological activities or physico-chemical properties of these substances. To overcome the problem of insufficient experimental data, the QSAR/QSPR approach can be applied to predict the missing information. These techniques, which use is recommended under the REACH regulation, also allow the screening and prioritisation of chemicals for experiments, with a consequent reduction of costs and of the number of tested animals. In this work the physico-chemical properties (Henry's law constant (LogH), melting point (T_M), sub-cooled liquid vapor pressure ($logP_L$), water solubility (logS), octanol-air partition coefficient ($logK_{OA}$) and octanol-water partition coefficient ($logK_{OW}$), photolysis degradation constant (k_p), and half-life (HL_p)), and the endocrine disrupting activity (aryl hydrocarbon receptor binding affinity, anti progestinic activity, T4-TTR competing potency and E2SULT inhibition potency) of 223 BFR have been modeled by QSAR. The experimental data available for the studied properties were taken from literature [1-5].
The here proposed models were developed according to the OECD principles for QSAR in the regulation of chemicals [6], thus particular attention was paid to the validation and the applicability domain of our new models. Reliable predictions for the studied endpoints were provided for all the BFRs belonging to the chemical domain of the models. The here presented QSPRs, could be used to fill data gaps according to the new REACH regulation, facilitating the screening and prioritisation of chemicals and the identification of more problematic compounds.

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

MATERIALS and METHODS

DATA SET The experimental data were taken from the literature [1-5]. The selected responses included physico-chemical properties (Henry's law constant (LogH), melting point (T_M), sub-cooled liquid vapor pressure ($logP_L$), water solubility (logS), octanol-air partition coefficient ($logK_{OA}$), octanol-water partition coefficient ($logK_{OW}$), photolysis degradation constant (k_p), and half-life (HL_p)), and the endocrine distrupting activity (aryl hydrocarbon receptor binding affinity, anti progestinic activity, T4-TTR competing potency and E2SULT inhibition potency). The experimental data set, very restricted in most of the cases, was formed by some PBDE congeners and other BFRs (i.e. BPA, TBBPA, HBCD).

MOLECULAR DESCRIPTORS

- 615 molecular descriptors (0D; 1D; 2D; 3D) were calculated by the software *DRAGON* [7].
- 4 quantum-chemical descriptors (Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO), HOMO-LUMO gap (DHL) and the ionisation potential (P ion)) were calculated by the semi empirical PM3 Hamiltonian for the geometry optimisation method available in the HYPERCHEM package [8].

MULTIPLE LINEAR REGRESSION MODELS and Variable Selection were performed by *Ordinary Least Squares* regression (OLS) method [9].

EXTERNAL VALIDATION

Prediction set selection based on the molecular structure (by Kohonen Maps - Artificial Neural Networks (K-ANN) [10]) or using the Random by response approach.

TOOLS OF VALIDATION AND DIAGNOSTICS

Models were developed taking into account the recently proposed OECD principles for QSAR validation [6].

- Internal (by Q^2_{LOO} and Q^2_{LMO}, Y-scrambling) and external validation (verified by Q^2_{ext}).
- Check of the quality of the best models by Residuals and Williams plot
- Applicability Domain (AD% for 223 BFRs) verified by leverage approach.

RESULTS

PHYSICO-CHEMICALS PROPERTY MODELS

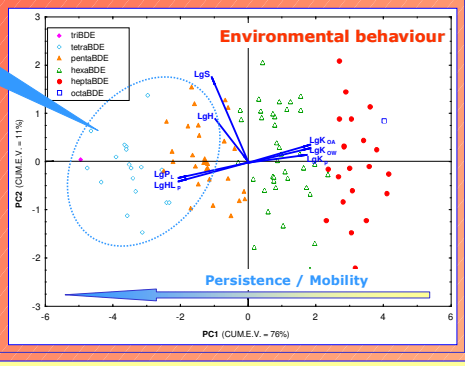
Endpoint	Obj. Tr.	Variables	R^2	Q^2_{LOO}	Q^2_{EXT}	$AD\%_{223}$
LogH	7	*BEHe7*	96.87	93.34	-	60.0
T_M	26	*X2A*	84.56	82.24	93.64	96.9
$LogP_L$	34	*T(O..Br)*	98.63	98.45	98.64	89.2
LogS	12	*Mor23m*	91.8	88.55	-	95.5
$LogK_{OA}$	30	*T(O..Br)*	97.37	96.78	99.55	87.9
$LogK_{OW}$	20	*T(O..Br)*	96.44	95.63	94.9	91.9
$LogK_p$	15	*MW*	94.91	93.83	-	91.0
$LogHL_p$	15	*T(O..Br)*	94.39	92.66	-	83.9

Principal Component Analysis

Tri-Penta BDE

- Higher volatility
- Higher persistence
- High lipofilicity 5.3 <$LogK_{OW}$< 7.2

Potential LRT ?!



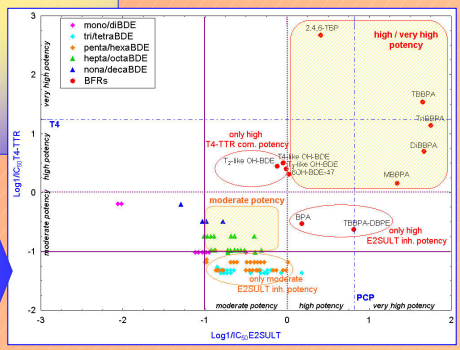
ENDOCRINE DISRUPTION ACTIVITY MODELS

Endpoint	Obj. Tr.	Variables	R^2	Q^2_{LOO}	Q^2_{EXT}	$AD\%_{223}$
Log1/RBA	18	*RDF035v RDF080v*	86.13	79.34	93.5	89.7
$Log1/IC_{50}$PRant	19	*GATS8e EEig09x*	83.45	76.85	79.9	95.5
$Log1/IC_{50}$T4-TTR	12	*MATS1v C-024*	98.69	97.44	-	96.9
$Log1/IC_{50}$E2SULT	16	*X5Av GATS2p*	87.96	83.69	-	98.7

Classification of BFRs based on predicted toxicity results
(according to Hamers *et al.*, 2006 [5])

Criteria	Potency
$Log1/IC_{50}$<-1	no/low
-1<$Log1/IC_{50}$<0	moderate
0<$Log1/IC_{50}$<+1	high
$Log1/IC_{50}$>+1	very high

E2SULT Inhibition Potency
Vs
T4-TTR Competing Potency



CONCLUSIONS

- Different QSAR models for prediction of physico chemical properties and endocrine disrupting potencies of BFRs, particularly PBDE, were proposed; the AD was verified for 223 BFRs. The developed models have good predictive power, and were verified by internal and, when possible, external validations.
- The combination of the predicted and experimental chemical-physical properties and degradation data by PCA allowed for the identification of a profile of the environmental behaviour of BFRs: tri - penta BDE were detected as the compounds of highest persistence and potential for long range transport.
- According to RBA experimental data [4], all predicted RBA values show weaker AhR affinity than the reference toxicant TCDD (< 2-5 orders of magnitude).
- T4-TTR competing potency seems greater for highly brominated diphenyl ethers (hepta-nonaBDEs), as well as for diBDEs, and for all the other BFRs, specially 2,4,6-TBP and TBBPA, whose TTR-binding potency exceeds that of the natural ligand T4.
- E2SULT inhibition potency appears moderate for almost all PBDEs (except mono-diBDEs) and high to very high for the other BFRs, particularly M/Di/Tri/TBBPA. These BFRs are more potent than the well-known inhibitor pentachlorophenol (PCP).
- According to the literature [5], a correlation was found between T4-TTR competing potency and E2SULT inhibition. In agreement with this, our models predicted a moderate and high toxicity respectively for highly brominated BDE congeners and BFRs with hydroxylated aromatic group.
- At this stage of the research it was not possible to define a quantitative dependency of toxicity from the number and the position of Br atoms in the molecules.

A new FP7-EU project (CADASTER) will model also flame retardants properties and activities for REACH regulation.

REFERENCES

1. Wania, F., Dugani, C.B. 2003. *Environ. Toxicol. Chem.* 22(6): 1252-1261
2. Tittlemier, S.A., Halldorson, T., Stern, G.A., Tomy, G.T. 2002. *Environ. Toxicol. Chem.* 21 (9): 1804-1810.
3. Eriksson, J., Green N., Marsh, G., Bergman, Å. 2004. *Environ. Sci. Technol.* 38: 3119-3125
4. Chen, G., Konstantinov, A.D., Chittim, B.G., Joyce, E.M., Bols, N.C., Bunce, N.J. 2001. *Environ. Sci.Technol.* 35:3749-3756
5. Hamers, T., Kamstra, J.H., Sonneveld, E., Murk, A.J., Kester, M.H.A., Andersson, P.L., Legler, J., Brouwer, A. 2006. *Toxicol. Sci.* 92:157-173
6. Available online at: http://www.oecd.org/document/23/ (accessed Sept. 2008)
7. Todeschini R., Consonni V. and Pavan M., 2001. *DRAGON – Software for the calculation of molecular descriptors*, rel. 1.12 for Windows. Free download available at http://www.disat.unimib/chm
8. HYPERCHEM. Release 7.03 for Windows, 2002. Hypercube, Inc. Florida, USA
9. Todeschini, R., 2001. *Moby Digs - Software for multilinear regression analysis and variable subset selection by Geneitc Algorithm*, rel. 2.3 for Windows, Talete srl, Milan (Italy)
10. J. Zupan, M. Novic, I. Ruisánchez. 1997. *Chemom. Int. Lab. Syst.*, 38 (1): 1-23