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

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SETAC New Orleans, Louisiana (USA)
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• 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:

- 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?
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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Model</th>
<th>Train obj.</th>
<th>Test obj.</th>
<th>Desc.</th>
<th>R²%</th>
<th>Q²&lt;sub&gt;LOO&lt;/sub&gt; %</th>
<th>Q²&lt;sub&gt;EXT&lt;/sub&gt; %</th>
<th>AD% on 220 BFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogK&lt;sub&gt;OA&lt;/sub&gt;</td>
<td>Full k-ANN Split</td>
<td>30</td>
<td>24</td>
<td>6</td>
<td>T(O..Br)</td>
<td>97.4</td>
<td>96.1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LogK&lt;sub&gt;OW&lt;/sub&gt;</td>
<td>Full k-ANN Split</td>
<td>20</td>
<td>14</td>
<td>6</td>
<td>T(O..Br)</td>
<td>96.4</td>
<td>97.1</td>
<td>-</td>
</tr>
<tr>
<td>MP</td>
<td>Full k-ANN Split</td>
<td>25</td>
<td>20</td>
<td>5</td>
<td>X2A</td>
<td>84.4</td>
<td>82.2</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LogP&lt;sub&gt;L&lt;/sub&gt;</td>
<td>Full k-ANN Split</td>
<td>34</td>
<td>28</td>
<td>6</td>
<td>T(O..Br)</td>
<td>98.7</td>
<td>98.8</td>
<td>-</td>
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<tr>
<td>LogS</td>
<td>Full</td>
<td>12</td>
<td></td>
<td></td>
<td>Mor23m</td>
<td>91.8</td>
<td>88.6</td>
<td>-</td>
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<tr>
<td>LogH</td>
<td>Full</td>
<td>7</td>
<td></td>
<td></td>
<td>BEHe7</td>
<td>96.9</td>
<td>93.3</td>
<td>-</td>
</tr>
<tr>
<td>LogKp*</td>
<td>Full</td>
<td>15</td>
<td></td>
<td></td>
<td>MW</td>
<td>94.9</td>
<td>93.8</td>
<td>-</td>
</tr>
<tr>
<td>LogHLp*</td>
<td>Full</td>
<td>15</td>
<td></td>
<td></td>
<td>T(O..Br)</td>
<td>94.4</td>
<td>92.7</td>
<td>-</td>
</tr>
</tbody>
</table>

*Photodegradation*

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Model for Log Koa

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

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

Are the predictions in the structural domain?

90.4 % into AD
**Comparison with existing models**

Predicted and Experimental data for 30 PBDEs

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>n° obj.</th>
<th>n° vars</th>
<th>R²%</th>
<th>Q²%</th>
<th>Q²_{EXT}</th>
<th>RMSE (30 obj.)</th>
<th>RMSE_{25 obj}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papa et al. (2009)</td>
<td>MLR</td>
<td>30</td>
<td>1</td>
<td>97,37</td>
<td>96,68</td>
<td>95,17</td>
<td>0,25</td>
<td>0,47</td>
</tr>
<tr>
<td>Xu et al. (2007)</td>
<td>MLR</td>
<td>22</td>
<td>2</td>
<td>97,61</td>
<td>97,25</td>
<td>-</td>
<td>0,31</td>
<td>0,23</td>
</tr>
<tr>
<td>Chen et al. (2003)</td>
<td>PLS</td>
<td>13</td>
<td>10</td>
<td>98,13</td>
<td>97,59</td>
<td>-</td>
<td>-</td>
<td>0,21</td>
</tr>
</tbody>
</table>

**Author**

- **Papa et al. (2009)**
- **Xu et al. (2007)**
- **Chen et al. (2003)**

**Method**

- MLR:
- PLS:

**n° obj.**

- 30
- 22
- 13

**n° vars**

- 1
- 2
- 10

**R²%**

- 97,37
- 97,61
- 98,13

**Q²%**

- 96,68
- 97,25
- 97,59

**Q²_{EXT}**

- 95,17
- -
- -

**RMSE (30 obj.)**

- 0,25
- 0,31
- -

**RMSE_{25 obj}**

- 0,47
- 0,23
- 0,21
Comparison with existing models

Predictions for 209 PBDEs

\[ \text{n° bromine increase} = \Delta \text{ increase} \]

\[ \Delta \text{ log units} \]

\[ \begin{align*}
\text{monoBDE} & \quad \text{diBDE} & \quad \text{triBDE} & \quad \text{tetraBDE} & \quad \text{pentaBDE} & \quad \text{hexaBDE} & \quad \text{heptaBDE} & \quad \text{octaBDE} & \quad \text{nonaBDE} & \quad \text{decaBDE} \\
\hline
\end{align*} \]

- \( Y_{\text{Papa}} = \text{Predictions by our model} \) (range Log Koa: 7.32 – 15.09)
- \( Y_{\text{Episuite}} = \text{Predictions by KoaWIN} \) (\( \Delta \text{max} = 3.33 \text{ log units}; \text{range Log Koa: 6.81-18.23} \))
- \( Y_{\text{Xu}} = \text{Predictions by Xu et al. (2007)} \) (\( \Delta \text{max} = 1.06 \text{ log units}; \text{range Log Koa: 7.4-15.73} \))
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 ($\text{LogP}_L$, $\text{LogKoa}$, $\text{LogKow}$, $\text{LogHL}_p$). 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

- Evaluation of environmental behaviour of BFRs

- 5 < LogK<sub>ow</sub> < 7

- Risk for tri-penta BDE!!

- Resistance to Photodegradation / Mobility
## RESULTS – QSAR models of Endocrine Disrupting Potency

### DATA SETS

<table>
<thead>
<tr>
<th>END-POINT</th>
<th>N° EXP DATA</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4-TTR comp</td>
<td>29</td>
<td>Hamers et al. (2006,2008)</td>
</tr>
<tr>
<td>E2SULT inh</td>
<td>29</td>
<td>Hamers et al. (2006,2008)</td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>POTENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response &lt; 20% of control</td>
<td>no potency</td>
</tr>
<tr>
<td>IC(_{50}) &gt; 10 µM &amp; resp &gt; 20% of control</td>
<td>low potency</td>
</tr>
<tr>
<td>1.0 µM &lt; IC(_{50}) &lt; 10 µM</td>
<td>moderate potency</td>
</tr>
<tr>
<td>0.1 µM &lt; IC(_{50}) &lt; 1.0 µM</td>
<td>high potency</td>
</tr>
<tr>
<td>0.01 µM &lt; IC(_{50}) &lt; 0.1 µM</td>
<td>very high potency</td>
</tr>
</tbody>
</table>

### CLASSES

1. **NO POTENCY**
2. **LOW/MODERATE POTENCY**
3. **(VERY) HIGH POTENCY**
**RESULTS – Endocrine Disruptor Potency**

**T4-TTR Competition**

<table>
<thead>
<tr>
<th>Model</th>
<th>K</th>
<th>n&lt;sub&gt;TR&lt;/sub&gt;</th>
<th>n&lt;sub&gt;p&lt;/sub&gt;</th>
<th>NER%</th>
<th>NER&lt;sub&gt;EXT&lt;/sub&gt;%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>3</td>
<td>29</td>
<td>-</td>
<td>93.1</td>
<td>-</td>
</tr>
<tr>
<td>Split</td>
<td>3</td>
<td>19</td>
<td>10</td>
<td>89.5</td>
<td>90</td>
</tr>
</tbody>
</table>

**E2SULT Inhibition**

<table>
<thead>
<tr>
<th>Model</th>
<th>K</th>
<th>n&lt;sub&gt;TR&lt;/sub&gt;</th>
<th>n&lt;sub&gt;p&lt;/sub&gt;</th>
<th>NER%</th>
<th>NER&lt;sub&gt;EXT&lt;/sub&gt;%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>1</td>
<td>29</td>
<td>-</td>
<td>89.6</td>
<td>-</td>
</tr>
<tr>
<td>Split</td>
<td>1</td>
<td>21</td>
<td>8</td>
<td>76.2</td>
<td>100</td>
</tr>
</tbody>
</table>
Applicability domain T4-TTR

- **Low/Moderate Potency**
  - Substituted

- **No Potency**
  - Substituted

- **Very High Potency**
  - [2,2',6,6']

Metabolites:
- Orto-substituted
- OH-Metabolites

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

<table>
<thead>
<tr>
<th>END-POINT</th>
<th>N° EXP DATA</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T_m</strong> Melting Point [°C]</td>
<td>25</td>
<td>Marsh <em>et al.</em> (1999); Tittlemier <em>et al.</em> (2002); Palm <em>et al.</em> (2002); Kuramochi <em>et al.</em> (2007)</td>
</tr>
<tr>
<td><strong>P_L</strong> Vapour Pressure [Pa, 25°C]</td>
<td>34</td>
<td>Wong <em>et al.</em> (2001); Palm <em>et al.</em> (2002); Wania and Dugani (2003)</td>
</tr>
<tr>
<td><strong>LogKoa</strong> Octanol-Air Partition Coef.</td>
<td>30</td>
<td>Harner and Shoeib (2002); Wania <em>et al.</em> (2002); Gouin and Harner (2003)</td>
</tr>
<tr>
<td><strong>LogKow</strong> Octanol-Water Partition Coef.</td>
<td>20</td>
<td>Palm <em>et al.</em> (2002); Wania and Dugani (2003); Braekevelt <em>et al.</em> (2003); Kuramochi <em>et al.</em> (2007)</td>
</tr>
<tr>
<td><strong>K_p</strong> Photodegradation Rate</td>
<td>15</td>
<td>Eriksson <em>et al.</em> (2004)</td>
</tr>
</tbody>
</table>