Human Bioaccumulation Potential Simulated in R and Implemented in KNIME

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Introduction and Aims
The assessment of human bioaccumulation potential is an important element in the risk assessment of chemicals. Tonnelier et al. (Arch Toxicol (2012) 86: 393–403) developed a generic physiologically based toxicokinetic (PBTK) model which, based on in vitro human liver metabolism data, minimal renal excretion and a constant exposure, was able to predict the bioaccumulation potential of chemicals. This model was designed to incorporate not only the chemical properties of the compounds, but also the processes that tend to decrease the concentration of the compound, such as metabolism. Following this work we have implemented the generic PBTK model, now written in R, in the open source KNIME interface.

Methods
The KNIME workflow consists of several nodes (Figure 1):
1. A database connection consisting of a connector;
2. A query filter node to select the values for the simulated chemical. In this specific node the MySQL database (version 5.5) is connected with the driver;
3. In parallel an XLS reader node reports the model parameters (e.g. flow rates, volume of organs, etc.) for input data into the model;
4. An R node where the PBTK model is described;
5. An R view node for output.

Based on Tonnelier et al. (2012) the simplified PBTK model was re-written in R. The three compartments (plus uptake) physiologically based model are reported here:

\[ V_{pr} \frac{dC_{sys}}{dt} = Q_{sys}(C_{sys} - C_{pr}) + k_{a}(t) \]
\[ V_{pr} \frac{dC_{liv}}{dt} = Q_{liv}(C_{liv} - C_{pr}) + Q_{liv}(C_{sys} - C_{liv}) - CL_{sys}C_{sys} \]
\[ V_{pr} \frac{dC_{sys}}{dt} = Q_{sys}(C_{sys} - C_{liv}) + Q_{sys}(C_{sys} - C_{liv}) - CL_{sys}C_{sys} \]
\[ \frac{dA}{dt} = -k_{a}(t) \]

Human bioconcentration factor hBCF \[ hBCF = \frac{C_{sys}}{D/T} V_{pr} / t \]

Results
The PBTK model implemented in the KNIME interface was used to simulate the systemic concentration at steady state (Csys) of chemicals (Figure 2) from which the hBCF was calculated (Table 1).

Figure 2. Simulation of the PBTK model at 0.01mg dose of compound.

Table 1. Csys values and hBCF values calculated with the KNIME interface.

<table>
<thead>
<tr>
<th>Name</th>
<th>Csys (µM)</th>
<th>hBCF (L*kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emamectin</td>
<td>21.3</td>
<td>375.3</td>
</tr>
<tr>
<td>PCB153</td>
<td>2.98</td>
<td>52.54</td>
</tr>
<tr>
<td>PCB155</td>
<td>2.98</td>
<td>52.53</td>
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</tr>
<tr>
<td>PCB87</td>
<td>2.98</td>
<td>52.53</td>
</tr>
<tr>
<td>Bentazone</td>
<td>0.71</td>
<td>16.43</td>
</tr>
<tr>
<td>Buprofezin</td>
<td>1.70</td>
<td>29.84</td>
</tr>
<tr>
<td>Fipronil</td>
<td>0.29</td>
<td>4.68</td>
</tr>
<tr>
<td>Flumethrin</td>
<td>0.35</td>
<td>6</td>
</tr>
<tr>
<td>Fenoxycarb</td>
<td>0.09</td>
<td>1.55</td>
</tr>
<tr>
<td>Fenvalerate</td>
<td>0.09</td>
<td>1.55</td>
</tr>
<tr>
<td>DDT</td>
<td>0.19</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Figure 3. hBCF calculated with the KNIME interface versus values obtained by Tonnelier et al., 2012.

Conclusions
• The human bioconcentration factor (hBCF) can be estimated using this new developed tool built using the KNIME interface!
• The hBCF calculated with KNIME interface were in the same order of magnitude as reported previously, but the potency ranking was slightly different; this will be investigated further!
• A direct and straightforward estimation of the hBCF based solely on a limited number of compound parameters would be of advantage in prioritisation of chemicals and may provide an efficient pre-screening criterion for a rapid assessment. This approach can be applied in the assessment of cosmetics ingredients!

Reference

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