Endpoint “Bioconcentration Factor” (BCF)

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Istituto di Ricerche Farmacologiche “Mario Negri”, Milano, Italy
Definition – substances

A substance is considered bioaccumulative if it biomagnifies in food chains.

Definition – processes

Bioaccumulation
uptake from the environment via any possible pathway

Biomagnification
uptake via foodweb resulting in increased concentrations in higher trophic levels

Bioconcentration
uptake from the surrounding phase via absorption, e.g. lipid diffusion
Stage | Description | Evaluation | Outcome
--- | --- | --- | ---
Step 1 | Food-web assessment | What food-web should be considered? | 
Step 2 | TMF assessment | Is TMF > 1? | B status confirmed
Step 3 | BMF assessment | Is BMF > 1? | B status probable
Step 4 | BCF/BAF assessment | Is BCF or BAF > 5000? | B status possible
Step 5 | Phys.-chem., ADME, Food-web model assessment | Is log Kow > 4, log Koa > 5, BMF > 1, TMF > 1? | B status potential

REACH ANNEX XIII

A substance fulfils the **bioaccumulation criterion (B-)** when:
– the bioconcentration factor (BCF) is higher than **2000**.

The assessment of bioaccumulation shall be based on measured data on bioconcentration in aquatic species. Data from freshwater as well as marine water species can be used.

A substance fulfils the **very bioaccumulative criterion (vB-)** when:
– the bioconcentration factor is greater than **5000**.
Comparison of quantitative B-criteria (BCF (BioConcentration Factor), BAF (BioAccumulation Factor), \(K_{\text{OW}}\) (1-octanol/water partition coefficient)).

<table>
<thead>
<tr>
<th>Institution/Authors</th>
<th>BCF</th>
<th>(\log K_{\text{OW}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al. 2007</td>
<td>---</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Brown &amp; Wania 2008</td>
<td>---</td>
<td>&gt; 3,5</td>
</tr>
<tr>
<td><strong>CLP Regulation</strong></td>
<td>&gt; 100</td>
<td>&gt; 3</td>
</tr>
<tr>
<td></td>
<td>&gt; 500</td>
<td>&gt; 4</td>
</tr>
<tr>
<td>OSPAR</td>
<td>&gt; 500</td>
<td>&gt; 4</td>
</tr>
<tr>
<td>CPA Green Screen</td>
<td>&gt; 1000</td>
<td>&gt; 4,5</td>
</tr>
<tr>
<td>Washington State</td>
<td>&gt; 1000</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>US EPA</td>
<td>&gt; 1000</td>
<td>---</td>
</tr>
<tr>
<td><strong>REACH</strong></td>
<td>&gt; 2000</td>
<td>&gt; 3, &gt; 4,5</td>
</tr>
<tr>
<td>ESIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEMI Schweden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK EPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm Convention</td>
<td>&gt; 5000</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>EU POP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environment Canada</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Question to stakeholders:

Which quantitative criterion should be focussed by OSIRIS?
BCF data quality
Many parameters may affect the experimental test:

**Test conditions:**
- Test typology (e.g.: OECD 305, etc ...
- Duration of uptake and depuration phase
- Exposure typology (e.g.: flow through, …)
- Tissue analysis (e.g.: total body, lipid content, specific tissue)
- Water conditions: temperature, particle/total or dissolved organic carbon contents, pH, etc.
- Light conditions (intensity, spectral quality)
- Detection method (e.g.: radio-label, analytical, etc ...)
- Incorrect use of radio-labelled compounds

**Properties of the chemical:**
- Physicochemical properties (Log Kow, water solubility)
- Toxicity
- Purity of chemical

**Organism used for the test:**
- Fish species, age, life stage, gender, size and physiological conditions (e.g.: lipid content, test organism health, etc...)
- Respiration rate and growth rate
BCF databases

Dimitrov
(Dimitrov et al., 2005)
- 511 compounds
- Single BCF value
- Log kow value

EURAS
(http://www.euras.be/)
- Gold standard
- 543 compounds
- Single or multiple BCF values
- Reliability score

Arnot
(Arnot et al., 2006)
- 842 compounds
- Single or multiple BCF values
- Reliability score
EURAS DS

Experimental variability

<table>
<thead>
<tr>
<th></th>
<th>n substances</th>
<th>max SD</th>
<th>average SD</th>
<th>max range</th>
<th>SD%&gt; 0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURAS (without DDT*)</td>
<td>542</td>
<td>1.40</td>
<td>0.30</td>
<td>3.57</td>
<td>37.08</td>
</tr>
</tbody>
</table>

* Very high variability (3.57 log units)

465 compounds with multiple values

Range < 0.4 log units for 60% of compounds

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### Arnot DS

#### Experimental variability

<table>
<thead>
<tr>
<th>Fish</th>
<th>Overall score</th>
<th>n substances</th>
<th>max SD</th>
<th>average SD</th>
<th>max range</th>
<th>% SD &gt; 0.3</th>
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</thead>
<tbody>
<tr>
<td>all</td>
<td>all</td>
<td>759</td>
<td>1.20</td>
<td>0.34</td>
<td>4.99</td>
<td>41.24</td>
</tr>
<tr>
<td>all</td>
<td>1</td>
<td>621</td>
<td>1.24</td>
<td>0.29</td>
<td>2.99</td>
<td>34.30</td>
</tr>
<tr>
<td>OECD</td>
<td>all</td>
<td>700</td>
<td>1.30</td>
<td>0.32</td>
<td>4.99</td>
<td>39.57</td>
</tr>
<tr>
<td>OECD</td>
<td>1</td>
<td>595</td>
<td>0.96</td>
<td>0.28</td>
<td>2.69</td>
<td>32.27</td>
</tr>
<tr>
<td>Oncorhynchus mykiss</td>
<td>all</td>
<td>117</td>
<td>0.82</td>
<td>0.26</td>
<td>2.72</td>
<td>27.35</td>
</tr>
<tr>
<td>Oncorhynchus mykiss</td>
<td>1</td>
<td>75</td>
<td>0.58</td>
<td>0.12</td>
<td>2.16</td>
<td>8.00</td>
</tr>
</tbody>
</table>

403 compounds with multiple values

Range < 0.4 log units (58% comp.)
Inter/intra databases experimental variability

300 common compounds → Range < 0.4 log units = 45%

Intra DB high variability

Inter DB high variability

Concordance

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2. Question to stakeholders:

How much uncertainty is acceptable?

Example later: how to combine evidences
(Q)SAR models for BCF

**objective:**
prediction of individual data, a piece of the ITS strategy

**LOGP BASED ESTIMATIONS**

• Worst-case function (Nendza, 1991)
  bilinear function describing the maximum BCF associated with a given lipophilicity

• Linear LogP functions
  e.g.: \( \text{LogBCF} = 0.76 \cdot \log P - 0.31 \)
Estimation software

• EPISuite

LogP based EPA tool to predict several environmental properties, including BCF (BCFBAF v3.00)

<table>
<thead>
<tr>
<th>LogP</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic compounds</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>LogBCF = 0.50</td>
</tr>
<tr>
<td>5 - 6</td>
<td>LogBCF = 0.75</td>
</tr>
<tr>
<td>6 - 7</td>
<td>LogBCF = 1.75</td>
</tr>
<tr>
<td>7 - 9</td>
<td>LogBCF = 1.00</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>LogBCF = 0.50</td>
</tr>
</tbody>
</table>

Non-ionic compounds

<table>
<thead>
<tr>
<th>LogP</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>logBCF = 0.50</td>
</tr>
<tr>
<td>1 - 7</td>
<td>logBCF = 0.6598*LogP - 0.333 + \sum correction factors</td>
</tr>
<tr>
<td>&gt; 7</td>
<td>logBCF = - 0.79*LogP + 7.554 + \sum correction factors</td>
</tr>
</tbody>
</table>
Estimation software

- CAESAR

\[ \text{Predicted LogBCF} \]
\[ \text{Experimental LogBCF} \]

- Training
  \[ R^2 = 0.84 \]
- Test
  \[ R^2 = 0.81 \]
- External
  \[ R^2 = 0.71 \]

www.caesar-project.eu

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BCF classification model
(objective: make an educated guess about chemicals who‘s experimental determination of BCF may be waived because it does not produce risk-relevant information or is unworkable to perform)
BCF classification model:

• The objective is to reliably identify nonB compounds based on multiple physico-chemical properties related to bioavailability.
• The optimised model is protective, i.e. no false negatives, though at the cost of false positives.
• The classification model can be formalised as a component of an ITS.
BCF classification parameter:

- lipophilicity
- water solubility
- volatility
- dissociation
- molecular charge
- molecular size
- degradability
BCF Datasets

» **test dataset:** CEFIC LRI compilation: 382 existing industrial chemicals
325 nonB, 57 B or vB (15 %); log BCF: -0.52 to 4.56; log $K_{OW}$: -2.13 to > 10; MW: 68 to 943 g/mol

» **validation dataset:** pesticides and new chemicals (confidential from UBA) 49 large complex structures
42 nonB, 7 B or vB (14 %); log BCF: 0.18 to 4.17; log $K_{OW}$: -0.89 to > 10; MW: 298 to 1061 g/mol

» **confirmation dataset:** 83 known B/vB chemicals
log $K_{OW}$: 0.08 to > 10; MW: 136 to 801 g/mol
Estimation software

- EpiSuite v4.0.
  based on fragment (substructure) methods
  [http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm](http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm)

- SPARC on-line calculator
  based on linear solvation energy relationships
  [http://ibmlc2.chem.uga.edu/sparc/](http://ibmlc2.chem.uga.edu/sparc/)
<table>
<thead>
<tr>
<th></th>
<th>log $K_{ow}$ &lt; 3</th>
<th>log $K_{ow}$ 3 - 4.5</th>
<th>log $K_{ow}$ 4.5 - 10</th>
<th>log $K_{ow}$ &gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Set: nonB</td>
<td>148</td>
<td>109</td>
<td>63</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>18</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>V-Set: nonB</td>
<td>2</td>
<td>9</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>C-Set: nonB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>3</td>
<td>77</td>
<td>1</td>
</tr>
</tbody>
</table>
The image depicts a scatter plot with the x-axis labeled as "% dissociation at pH 7 (SPARC)" and the y-axis labeled as "log BCF". The data points are distributed across the graph, indicating a relationship between the two variables.
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Classification statistics:

Accuracy (overall performance): \[ \frac{(TP + TN)}{Tot} \times 100 \]

Sensitivity (false negatives): \[ \frac{TP}{TP + FN} \times 100 \]

Specificity (false positives): \[ \frac{TN}{TN + FP} \times 100 \]

Efficacy (true negatives): \[ \frac{TN}{Tot} \times 100 \]
### Classification statistics:

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>log $K_{OW}$ T-Set</td>
<td>55.0 %</td>
<td>100 %</td>
<td>47.1 %</td>
<td>40.1 %</td>
</tr>
<tr>
<td>log $K_{OW}$ V-Set</td>
<td>36.7 %</td>
<td>100 %</td>
<td>26.2 %</td>
<td>22.4 %</td>
</tr>
<tr>
<td>Dissociation T-Set</td>
<td>25.7 %</td>
<td>100 %</td>
<td>13.8 %</td>
<td>11.5 %</td>
</tr>
<tr>
<td>Dissociation V-Set</td>
<td>28.6 %</td>
<td>100 %</td>
<td>17.1 %</td>
<td>14.3 %</td>
</tr>
<tr>
<td>Henry Constant T-Set</td>
<td>18.3 %</td>
<td>100 %</td>
<td>4.0 %</td>
<td>3.4 %</td>
</tr>
<tr>
<td>Henry Constant V-Set</td>
<td>49.0 %</td>
<td>100 %</td>
<td>40.5 %</td>
<td>34.7 %</td>
</tr>
<tr>
<td>Hydrolysis T-Set</td>
<td>22.0 %</td>
<td>100 %</td>
<td>8.3 %</td>
<td>7.1 %</td>
</tr>
<tr>
<td>Hydrolysis V-Set</td>
<td>59.2 %</td>
<td>100 %</td>
<td>52.4 %</td>
<td>44.9 %</td>
</tr>
<tr>
<td>Biodegradability T-Set</td>
<td>27.7 %</td>
<td>100 %</td>
<td>15.1 %</td>
<td>12.8 %</td>
</tr>
<tr>
<td>Biodegradability V-Set</td>
<td>16.3 %</td>
<td>100 %</td>
<td>2.4 %</td>
<td>2.0 %</td>
</tr>
<tr>
<td>Combined model T-Set</td>
<td>67.8 %</td>
<td>100 %</td>
<td>62.2 %</td>
<td>52.9 %</td>
</tr>
<tr>
<td>Combined model V-Set</td>
<td>79.6 %</td>
<td>100 %</td>
<td>76.2 %</td>
<td>65.3 %</td>
</tr>
</tbody>
</table>
Applicability domain check:
- polybrominated compounds
- alkylated heavy metals
- thiols
- sulfonates

T-Set: 382 (100 %)

V-Set: 49 (100 %)

230 (60.2 %)

38 (77.6 %)

213 (55.8 %)

37 (75.5 %)

203 (53.1 %)

29 (58.2 %)

193 (50.5 %)

17 (34.7 %)

180 (47.1 %)

17 (34.7 %)

log Kow < 3
log Kow > 10

no

yes

ready biodegradability

no

yes

log HLC < -11 atm/(mol/L)

no

yes

log K_mfd < 1 L/(mol sec)

no
dissociation at pH 7 > 5 %

no

tendence possible on nonB/B/vB properties

no

robust evidence for nonB properties

T-Set: 202 (52.9 %)

V-Set: 32 (65.3 %)

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Summary of the BCF classification model:

• The combined classification model reliably identifies nonB compounds based on multiple physico-chemical properties related to bioavailability.
• The optimised model is protective, i.e. no false negatives, though at the cost of false positives.
• Classification statistics indicate about 60 % reduction potential in BCF testing.
• The external validation confirms favourable performance.
• The confirmation dataset (B/vB compounds) served to define the limits of the applicability domain of the classification model.
• The combined classification model can become a powerful component in an ITS (Integrated Testing Strategies) framework for the identification of bioaccumulative (B/vB) chemicals under REACH.
What is an ITS?

**Alternative methods data**
- In-silico
- In-vitro
- ...

**Experimental data**
- Animal welfare
- Costs, logistics and limitation to tests

**Waiving**

**Integration of all available information**

**Integrated Testing Strategy (ITS)**

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Conceptual scheme

Are reliable BCF values available?

- Y: Perform C&L (using logP)
- N: Stop

Is < 10 t/y?

- Y: Stop
- N: Is > 100 t/y?

Is > 100 t/y?

- Y: Evidence for degradation and/or metabolism?
- N: Can the substance be vP or P?

Evaluate if products are relevant for BCF assessment

<table>
<thead>
<tr>
<th>t/y</th>
<th>C&amp;L</th>
<th>B and vB</th>
<th>CSA</th>
<th>BCF value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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Waiving is possible (e.g. using the BCF classification model)?

- **Y**: nB
- **N**: Perform C&L (using logP)

Is the substance ionisable?

- **Y**: Use ad-hoc methods (QSAR, SPMD/SPME, Alternatives)
- **N**: Perform alternative methods

Are reliable BAF or BMF data available and they indicate that the substance is B (or vB)?

- **Y**: Is < 100 t/y?
  - **Y**: The substance is B (or vB) **Stop**
  - **N**: Perform alternative methods
- **N**: The substance is B (or vB) **Stop**
Are you able to obtain reliable BCF values performing an *in-silico* or an *in-vitro* method?

- **Y**
  - Are other data available and are all the data concordant?
    - **Y** Stop
    - **N**
      - Is > 100 t/y?
        - **Y**
          - Do the OECD 305 test or mollusc BCF test
        - **N**
          - Do the limited BCF test for fish or the OECD 305 test or mollusc BCF test
      - **N**
        - Do dietary bioconcentration test
  - **N**
    - • log P < 6 or
      - • logP > 6 and test tech. requirements fulfilled or
      - • water solubility > 0.1 mg/l?
        - **Y**
          - Do the limited BCF test for fish or the OECD 305 test or mollusc BCF test
        - **N**
          - Do dietary bioconcentration test

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Uncertainty and combination of data
(example kindly provided by Universitat Rovira i Virgili – Tarragona)

1,2,3,4-tetrachloro-benzene

<table>
<thead>
<tr>
<th>Data source</th>
<th>Reliability weight</th>
<th>log BCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURAS</td>
<td>0.47</td>
<td>3.2</td>
</tr>
<tr>
<td>Arnot</td>
<td>0.53</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Combined**

<table>
<thead>
<tr>
<th>Data source</th>
<th>Basic probability assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>m {nB}</td>
<td>m {B}</td>
</tr>
<tr>
<td>Combined</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**Data source Reliability score**

<table>
<thead>
<tr>
<th>Data source</th>
<th>Reliability score</th>
<th>log BCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURAS</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Arnot</td>
<td>1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Arnot**

<table>
<thead>
<tr>
<th>Data source</th>
<th>Reliability weight</th>
<th>m {nB}</th>
<th>m {B}</th>
<th>m {vB}</th>
<th>m {nB, B, vB}</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURAS</td>
<td>0.47</td>
<td>0.50</td>
<td>0</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Arnot</td>
<td>0.53</td>
<td>0.18</td>
<td>0.55</td>
<td>0.09</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**Combined**

<table>
<thead>
<tr>
<th>Data source</th>
<th>Basic probability assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>m {nB}</td>
<td>m {B}</td>
</tr>
<tr>
<td>Combined</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Uncertainty and combination of data  
(example kindly provided by Universitat Rovira i Virgili – Tarragona)

<table>
<thead>
<tr>
<th>name</th>
<th>EURAS 2</th>
<th>EURAS 3</th>
<th>EURAS 4</th>
<th>Arnot 1</th>
<th>Arnot 2</th>
<th>Arnot 3</th>
<th>Arnot 4</th>
<th>Arnot 5</th>
<th>Arnot 6</th>
<th>Arnot 7</th>
<th>Arnot 8</th>
<th>Arnot 9</th>
<th>Arnot 10</th>
<th>combined probability assignment (m_b)</th>
<th>Readily</th>
<th>Not Readily</th>
<th>Readily, Not Readily</th>
<th>length of belief–plausibility intervals</th>
<th>Biowin5</th>
<th>CERI</th>
<th>Biowin5</th>
<th>CERI</th>
<th>uncertainty reduction (%)</th>
<th>decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloromethane</td>
<td>0.47</td>
<td>0.21</td>
<td>0.32</td>
<td>0.47</td>
<td>0.79</td>
<td>0.21</td>
<td>0.53</td>
<td>0.4</td>
<td>0.6</td>
<td>0.32</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.47</td>
<td>0.47</td>
<td>0.21</td>
<td>0.53</td>
<td>0.47</td>
<td>0.6</td>
<td>0.32</td>
<td>20</td>
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Uncertainty Reduction in Environmental Data with Conflicting Information
The webtool (developed by SIMPPLE)

http://osiris.simpple.com
Some features of the webtool

✅ **Substance management**: create, edit, delete substances

✅ **Study record management** (*in vivo*, *in vitro* and *in silico* test data, phys-chem. data), ITS oriented

✅ **ITS management** (assessment) and execution

✅ **BCF, mutagenicity, skin sensitization and aquatic toxicity**

✅ **IUCLID5 import**. Partial support, only data relevant to ITS

✅ **Weight of Evidence approach** (WoE). Integration of Consensus models: Bayesian Nets and Dempster-Shafer model

✅ **OSIRIS database integration**. Integration with datasets included in ChemProp

✅ **Access to the Chemical Space Navigation** tool developed by URV

✅ **Framework for user manual** and contextual help
How it works

1. Create a substance. Substances are identified by a name, and its CAS number has to be provided.

2. Add study records of the substance. Study records are tests (in vivo and in vitro), QSAR’s and physico-chemical properties. Direct input and IUCLID5 import.

3. Create an assessment on the substance, selecting the desired endpoint and the information requirements.

4. Execute the assessment, and follow its guidance to reach a conclusion.
Thank you very much for your attention!

Questions?
Comments?