Introduction

Safety assessment of industrial chemicals in Japan is carried out based on the Chemical Substances Control Law (CSCL). The government has been taking responsibility for carrying out safety assessments of the 20,000 chemicals to which the CSCL currently applies; however, it has measured about 1,600 chemicals in the past 30 years. It is clearly not realistic, in view of cost and time, to test all previously untested chemicals. Use of the category approach and Quantitative Structure-activity relationship (Q SAR) is regarded as a promising alternative to actual tests. However, no predictive method has yet been established for bioconcentration of general chemicals using the category approach. In the present study, we have developed categories based on mechanistic rationales for predicting the bioconcentrations of chemicals based on BCF data on existing chemicals under CSCL in Japan.

Materials and Methods

Data set

The CSCL bioconcentration test is conducted as a part of Method 305, established under the Organization for Economic Co-operation and Development (OECD) guidelines for testing chemicals. The test fish (carp) are exposed to two concentrations of the test chemical in water, under flow-through conditions. We obtained BCF values for fish from the CSCL database[1] and screened 371 chemicals for categorization, whose test concentrations are lower than their solubility in water.

Parameters

Nine parameters relevant to the bioconcentration for chemicals were used to investigate the predictive approach of each category (Table 1).

Results and Discussion

The Concept of the Category for Bioconcentration in Fish

In view of the bioconcentration mechanism, the bioconcentration of chemicals in fish could be categorized according to the following three factors:

1. The mechanism of absorption (e.g., passive diffusion, active transport, the paracellular pathway and endocytosis)
2. The interactions between molecules in living tissue (e.g., the Van der Waals force, dipole-dipole interaction, hydrogen-bonding interaction and ion interaction)
3. The reactive property of chemicals in living tissue (e.g., protein binding and metabolism).

Category I: chemicals without any polar functional groups

The correlation between logPow and logBCF for the chemicals with logPow < 6 and with 8 Å < Dmax < 11 Å was close. The regression equations were obtained.

\[ \text{logPow}_{(\text{calculated value})} = 0.18 \times \text{logPow}_{(\text{observed value})} + 0.82 \]

Category II-A: chemicals with a polar functional group (hydrogen acceptor)

The dipole-dipole interaction of chemicals placed in Category II-A is not an important factor in their bioconcentration. We therefore conclude that the BCF value of most chemicals in Category II-A can be predicted by using the same correlation equation as for Category I.

\[ \text{logPow}_{(\text{calculated value})} = 0.18 \times \text{logPow}_{(\text{observed value})} + 0.82 \]

Category II-B: chemicals with a polar functional group (hydrogen donor)

A multiple regression analysis was conducted on the observed logBCF values of the chemicals placed in Category II-B using the nine parameters. However, no significant correlation could be obtained between logBCF and these parameters. The logBCF of most chemicals in Category II-B falls below the 95% confidence limit of the equation for Category I, implying the effect of the hydrogen bonding to biomembrane.

Category III: ionic chemicals

Acid dissociation constant (pKa) and logD were investigated as parameters describing the influence of ionic interaction. However, the correlation between logBCF value and these parameters of the Category III was weak.

On the other hand, linear-chain carboxylic acids in this category with the same logPow level show the same logBCF value. This suggests that data gap filling by read-across for chemicals placed in Category III is feasible.

Table 1. Parameters relevant to the bioconcentrations of chemicals

<table>
<thead>
<tr>
<th>Parameters</th>
<th>logPow (observed value), logPow (calculated value)</th>
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</thead>
<tbody>
<tr>
<td>Dmax (minimum diameter of the sphere that would enclose the molecule), Å²</td>
<td>11Å, 8Å</td>
</tr>
<tr>
<td>p (square of dipole moment)</td>
<td>10Å², 8Å²</td>
</tr>
<tr>
<td>BCR (molecular Refraction, a value proportional to polarizability)</td>
<td>6Å², 7Å²</td>
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<tr>
<td>TPSA (Topological Polar Surface Area)</td>
<td>8Å², 11Å²</td>
</tr>
<tr>
<td>Hy (Number of hydrogen bond acceptor atoms)</td>
<td>4Å², 6Å²</td>
</tr>
<tr>
<td>pKa (observed value), pKa (calculated value)</td>
<td>2Å², 4Å²</td>
</tr>
<tr>
<td>logD (calculated value)</td>
<td>2Å², 4Å²</td>
</tr>
</tbody>
</table>

*1) KOWWIN ver. 1.07 (U.C. EPA) *2) Database Manager ver. 1.3: (Dassl UAC) *3) Conversion model: Automated DASIL, Conformer generation: Rapid Calculation method: AM1 *4) MOE2009.10: (Chemical Computing Group, Inc.) *5) Hy, Hy don, and Hy, don are used together as a set. *6) If the pKa value for a chemical was not measured, the value was calculated using ACD/pka v2.2 (Advanced Chemistry Development, Inc.)