Evaluation of Bioconcentration Factors by Category Approach for Chemicals

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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 relationships [(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 (Table1).

Table1. Parameters relevant to the bioconcentrations of chemicals

Parameters
logPow (observed value), logPow (calculated value)*1
Dmax (minimum diameter of the sphere that would enclose the molecule)*2
μ^2 (square of dipole moment)*2
MR (Molecular Refraction, a value proportional to polarizability(α))*3
TPSA (Topological Polar Surface Area)*3
Hy_acc (Number of hydrogen bond acceptor atoms)*3,4
Hy_don (Number of hydrogen bond donor atoms)*3,4
pKa (observed value), pKa (calculated value)*5
logD (calculated value)*1,5

*1 KOWWIN ver.1.67. (US EPA)
*2 Database Manager ver.1.3. (OASIS LMC) The conditions of conversion: Conversion mode: Automated OASIS; Conformer generation: Rapid; Calculation method: AM1.
*3 MOE2009.10. (Chemical Computing Group, Inc.)
*4 Hy_acc and Hy_don are used together as a set.
*5 If the pKa value for a chemical was not measured, the value was calculated using ACD pKa DB ver.12.0 (Advanced Chemistry Development, Inc.)

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 ionic 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 8Å < Dmax < 11Å was close. **The regression equations were obtained.**

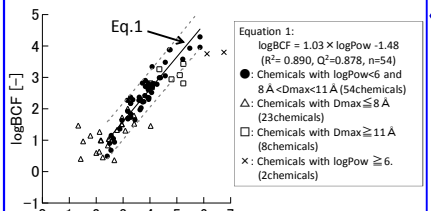

Fig.1 The relationship between logPow and logBCF for chemicals placed in Category I.

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.**

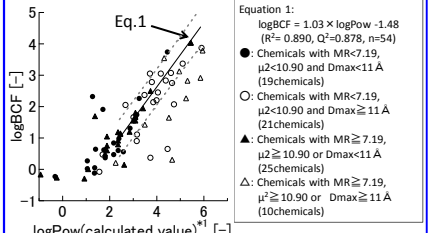

Fig.2 The relationship between logPow and logBCF for chemicals placed in Category II-A.

In these categories, the chief mechanism of chemical uptake by fish is biomembrane penetration by passive diffusion

I
Principal interaction between molecules:
- **Van der Waals' force**

(e.g., aliphatic and halogenated hydrocarbons)

II-B
Principal interactions between molecules:
- **Van derWaals' force**
- **Dipole-Dipole interaction**
- **Hydrogen-bond interaction**

(e.g., alcohol, amido.)

II-A
Principal interactions between molecules:
- **Van derWaals' force**
- **Dipole-Dipole interaction**

(e.g., ether, ketone.)

III
Principal interactions between molecules:
- **Ion-Ion interaction**

(e.g., carboxylic and sulfonic acids)

High reactivity in vivo.

IV
These chemicals **bind protein molecules** (e.g., thiols)

V
These chemicals are **readily metabolized in living tissue** (e.g., esters)

Chemical uptake by fish via mechanisms other than passive diffusion through biomembranes

VI
Uptake mechanism is **paracellular transport or active transport** (e.g., proteins and amino acids)

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.

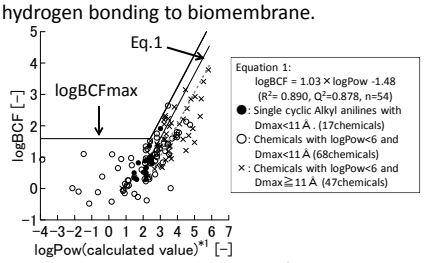

Fig.3 The relationship between logPow and logBCF for chemicals placed in Category II-B.

Therefore, we studied the prediction by using read across. Single cyclic alkyl anilines in this category with the same logPow level show approximately the same logBCF value. **An example of this for single cyclic alkyl anilines using the read-across** is shown Table 2.

Table2 Example of data gap filling for single cyclic alkyl anilines using read-across

No.		Untested chemical	1	2
CAS No.		**95-53-4**	95-68-1	95-78-3
Molecular Structure				
logBCF		**0.40 (read across)**	0.50 (observed value)	0.30 (observed value)
Dmax*2 [Å]		**8.0**	9.0	9.0
logPow	observed value	**1.33**	1.68	1.87
	calculated value*1	**1.62**	2.17	2.17

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.**

Category V: *chemicals that are readily metabolized in living tissue*

Thirty-six chemicals of the 371 chemicals, such as **esters and organophosphates, were placed in Category V.** It would be difficult to estimate metabolic rate to predict BCF quantitatively. [2, 3]. **Read across would be useful for the prediction of chemicals in the category.** For example, organophosphates in this category having a same level of logPow show a same level of logBCF value.

[1] Japan CHEmicals Collaborative Knowledge database(J-CHECK), NITE, 2008, Available at: http://www.safe.nite.go.jp/jcheck/english/detail.action?cno=36437-37-3&mno=5-3604
[2] J.A. Arnot, D. Mackay, M. Bonnell, *Estimating metabolic biotransformation rates in fish from laboratory data*, Environ Toxicol Chem, **27**(2008), pp.341-351.
[3] S. Dimitrov, N. Dimitrova, T. Parkerton, M. Comber, M. Bonnell, O. Mekenyan., *Base-line model for identifying the bioaccumulation potential of chemicals.*, SAR QSAR Environ Res, **16**(2005), pp.531-54.