Use of read-across for the assessment of biodegradation and bioaccumulation potential of chemicals under Japan Chemical Substances Control Law

June 2016

National Institute of Technology and Evaluation, Japan
Chemical Management Center

Topics

Use of read-across for the assessment under the Japan Chemical Substances Control Law (CSCL);

1. Biodegradation assessment
2. Bioaccumulation assessment
   - 2.1 Evaluation method using analogy rule
   - 2.2 Evaluation method using logD

1. BIODEGRADATION ASSESSMENT

Concept of read-across for the biodegradation assessment under the CSCL

- ✓ The biodegradability of untested chemicals is assessed by using the experimental data of source chemicals.
- ✓ The source chemical used for read-across under the CSCL is defined as similar chemical on the basis of the following two factors related to metabolism of microorganism.
  - Structural similarity (eg. Basic skeleton, organic functional group and its substitution position)
  - Chemico-physical properties (eg. resolvability and stationarity in water)

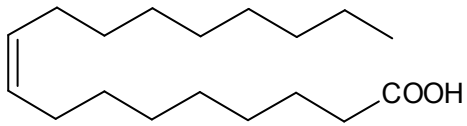
Use of read-across for the biodegradation assessment under the CSCL

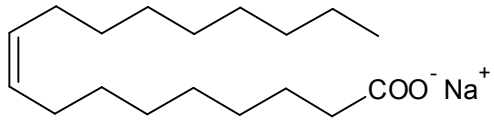
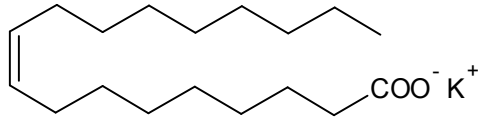
- ✓ In the review of the biodegradation assessment of chemicals under the CSCL, the read-across is accepted as the following major two types;
  - A) Target chemical and source chemicals are the relationship between the acid and its salts, such as metallic and ammonium salt.
  - B) If there exist two or more similar chemicals whose biodegradation test data are available, it is considered that the biodegradation potential of a target chemical is evaluated by interpolating data.

Case study (Rule A)

The relationship between the acid and its salts

→Target chemicals are assessed as **"Readily biodegradable"** by read-across.

	Source chemical
Chemical name	Oleic acid
CAS No.	112-80-1
MITI No.	2-609, 2-975
Structure	
Biodegradability	Readily biodegradable (Pub. Date: 1993/12/28) Biodegradation test data Method: OECD TG 301C Term: 28 days Degradation value: BOD : 78%, GC : 100%

	Target chemical 1
Chemical name	Sodium (Z)-oleate
CAS No.	143-19-1
MITI No.	2-611
Structure	
Biodegradability	Readily biodegradable (Read-across)
	Target chemical 2
Chemical name	Potassium (Z)-oleate
CAS No.	143-18-0
MITI No.	2-611, 9-1677
Structure	
Biodegradability	Readily biodegradable (Read-across)

*METI website (Japanese only):
http://www.meti.go.jp/committee/summary/0004475/pdf/118_02_02.pdf

Case study (Rule B)

	Source chemical 2	Source chemical 3	Source chemical 4	Source chemical 5
Chemical name	Octan-1-ol	Tridecyl alcohol	Hexadecan-1-ol	1-hexacosanol
CAS No.	111-87-5	112-70-9	36653-82-4	506-52-5
MITI No.	2-217	2-217	2-217, 2-3704	2-217
Structure	$CH_3(CH_2)_7OH$	$CH_3(CH_2)_{12}OH$	$CH_3(CH_2)_{15}OH$	$CH_3(CH_2)_{25}OH$
Biodegradability	Biodegradation test information (OECD TG 301C, 28 days)			
	Readily biodegradable			
	Degradation value: BOD : 89% GC : 100% Pub. Date: 2002/11/08	Degradation value: BOD : 88% GC : 100% Pub. Date: 1978/12/12	Degradation value: BOD : 86% GC : 95% Pub. Date: 2002/03/26	Degradation value: BOD : 75% GC : 97% Pub. Date: 1982/12/28

Target chemicals are assessed as **"Readily biodegradable"** by interpolating data.

	Target chemical 3	Target chemical 4	Target chemical 5
Chemical name	Decan-1-ol	1-Eicosanol	1-Docosanol
CAS No.	112-30-1	629-96-9	661-19-8
MITI No.	2-217	2-217	2-217
Structure	$CH_3(CH_2)_9OH$	$CH_3(CH_2)_{19}OH$	$CH_3(CH_2)_{21}OH$
Biodegradability	Readily biodegradable (Read-across)		

*METI website (Japanese only):
http://www.meti.go.jp/committee/summary/0004475/pdf/122_01_03.pdf

Use of read-across for the risk assessment of chemicals under the CSCL

121 existing chemicals were assessed as "Readily biodegradable" by read-across in order to perform the risk assessment under the CSCL.

Financial year	Number of existing chemicals
2010	2
2011	4
2012	106
2013	9
Total	**121**

2. BIOACCUMULATION ASSESSMENT

Use of read-across for the bioaccumulation assessment under the CSCL

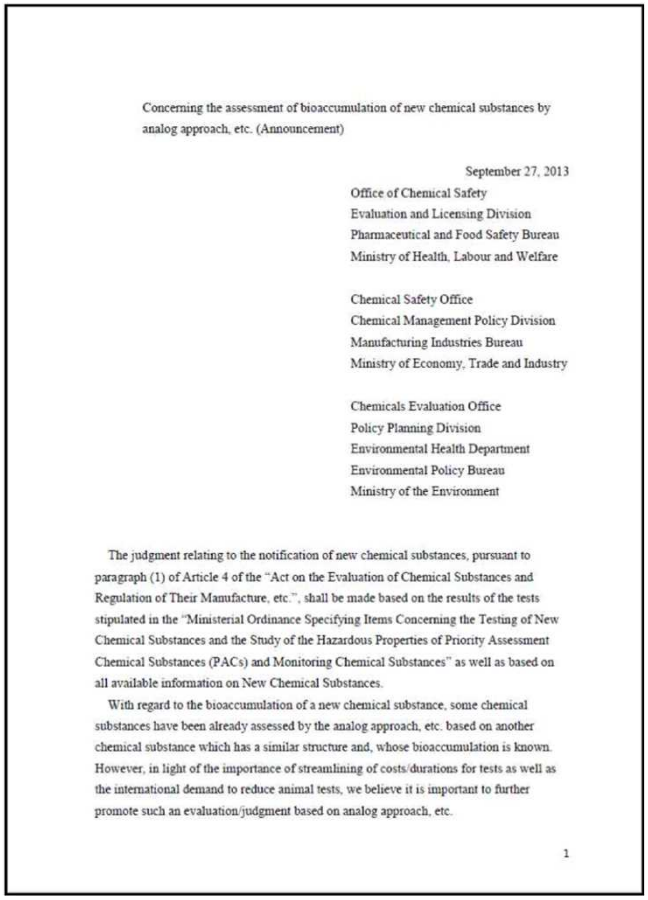
- ✓ In the bioaccumulation assessment of chemicals under the CSCL, the read-across was accepted as the following major four types;
  - ○ 2.1 Bioaccumulative analogy rule*3
  - ○ 2.2 Log D < 2.5 (in case of the ionic substance only)
  - 2.3 MW ≥ 800 (When a chemical contain two or more halogen element, MW ≥ 1,000)
  - 2.4 Log P < 3.5

*3 The use on the basis of the structural similarity or the comparison of hydrophily

2.1 BIOACCUMULATIVE ANALOGY RULE

Bioaccumulative analogy rule is announced in September 2013

- ✓ Ministry of Economy, Trade and Industry in Japan (METI) announced a new guidance of the bioaccumulation assessment by using analogous and QSAR, **to clarify the criteria for judgement of the analogue approach for the bioaccumulation assessment under the CSCL.**



Concerning the assessment of bioaccumulation of new chemical substances by analog approach, etc. (Announcement)

September 27, 2013

Office of Chemical Safety
Evaluation and Licensing Division
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Chemical Safety Office
Chemical Management Policy Division
Manufacturing Industries Bureau
Ministry of Economy, Trade and Industry

Chemicals Evaluation Office
Policy Planning Division
Environmental Health Department
Environmental Policy Bureau
Ministry of the Environment

The judgment relating to the notification of new chemical substances, pursuant to paragraph (1) of Article 4 of the "Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc.", shall be made based on the results of the tests stipulated in the "Ministerial Ordinance Specifying Items Concerning the Testing of New Chemical Substances and the Study of the Hazardous Properties of Priority Assessment Chemical Substances (PACs) and Monitoring Chemical Substances" as well as based on all available information on New Chemical Substances.

With regard to the bioaccumulation of a new chemical substance, some chemical substances have been already assessed by the analog approach, etc. based on another chemical substance which has a similar structure and, whose bioaccumulation is known. However, in light of the importance of streamlining of costs/durations for tests as well as the international demand to reduce animal tests, we believe it is important to further promote such an evaluation/judgment based on analog approach, etc.

1

http://www.meti.go.jp/policy/chemical_management/english/files/laws/bioaccumulation_analog_approach.pdf

New guidance on bioaccumulation assessment by using analogue approach and QSAR

Bioaccumulation assessment by using;

A) Read-across and QSAR.

B) Read-across and the comparison of hydrophilicity (polarity) by HPLC.

(Rule A) Bioaccumulation assessment by using read-across and QSAR

If chemical A meets the following criteria, chemical A can be assessed to be **"not highly bioaccumulative"**:

(1) Chemical A is similar in structure to chemical B. (specifically as follows):
   i. Chemical A has the same basic skeleton as chemical B and chemical A's structure is partially changed from chemical B, or
   ii. Chemical A is an isomer of chemical B.

(2) Measured BCF of chemical B is below 500.

(3) Bioaccumulation of chemical A is estimated in a rational way to be almost the same as or lower than chemical B based on their chemical structure. (specific conditions as follows)
   i. Calculated BCF by using QSAR of chemical A is almost the same as or lower than measured and calculated BCF of chemical B.
   ii. Two or more similar chemical B have measured BCF <100.

*4 Recommended QSAR model is either BCFBAF (EPI SUITE) or BCF base-line model (OASIS CATALOGIC).

*5 Japan added the published measured BCF data on the website in this month in order to facilitate the above approach. http://www.nite.go.jp/en/chem/qsar/cscl_data.html

Example (1)

Chemical A is "not highly bioaccumulative" in both cases.

Case 1

(1) Chemical Structure

Chemical A ⟷ (Similar) Chemical B

(2) Measured BCF

Chemical B → BCF < 500

(3) Calculated BCF by using QSAR

QSAR BCF Chemical A < QSAR BCF Chemical B

Case 2

(1) Chemical Structure

Chemical A ⟷ (Similar) Chemical B, Chemical C

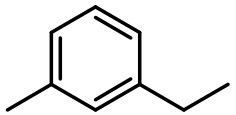
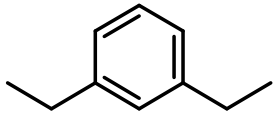
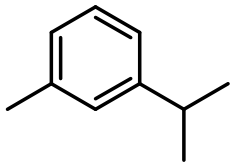
(2) Measured BCF

Chemical B → BCF < 100

Chemical C → BCF < 100

Case study (Rule A)

- ✓ Source chemicals and target chemical fulfil three conditions of the analogy rule A (See page 14 and 15).
- ✓ The bioaccumulation potential of target chemical can be judged **"not highly bioaccumulative*1"** under the CSCL.

Name	Structure	Calculated BCF*2	Measured BCF
Target chemical		196	**Not highly bioaccumulative**
Source chemical 1		481	485
Source chemical 2		433	491

*1 CSCL defines "Not highly bioaccumulative" as BCF less than 5,000.
*2 Calculated by BCFBAF v.3.01(US EPA)

(Rule B) Bioaccumulation assessment based on the comparison of hydrophilicity (Polarity) by HPLC.

If chemical A meets the following criteria, chemical A can be assessed to be **"not highly bioaccumulative"**:

(1) Chemical A is similar in structure to chemical B. (specifically as follows):

i. Chemical A has the same basic skeleton as chemical B and chemical A's structure is partially changed from chemical B, or

ii. Chemical A is an isomer of chemical B.

(2) Measured BCF value of chemical B is below 500.

(3) It is observed that chemical A is more hydrophilic (polar) than chemical B by reversed-phase HPLC.

＊ This analogous method does not apply to surfactants, organic metallic compounds, low purity compound and inorganic compound.

Example (2)

Chemical A is "not highly bioaccumulative".

Case 3

(1) Chemical Structure

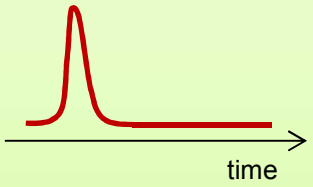
Chemical A ⟷ (Similar) Chemical B

(2) Measured BCF

Chemical B → BCF < 500

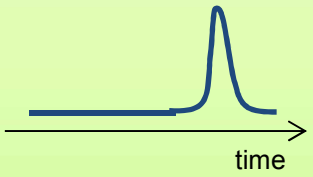
(3) Comparison of Hydrophilicity (Polarity) by reversed-phase HPLC

Chemical A



more hydrophilic

Chemical B



less hydrophilic

Case study (Rule B)

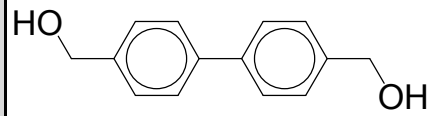
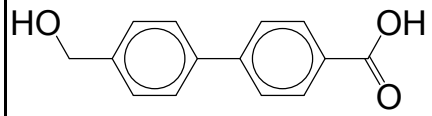
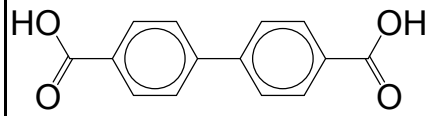
- Target Chemicals and Endpoint -

✓ Target chemicals:

Biodegradation/hydrolysis products of 4, 4'-Bis-(chloromethyl) -1, 1'-biphenyl (source chemical 1) in the biodegradation test (OECD TG 301C).

✓ Target Endpoint:

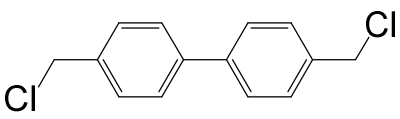
Bioaccumulation potential

	Target chemical 1 (Biodegradation/hydrolysis Product 1)	Target chemical 2 (Biodegradation Product 2)	Target chemical 3 (Biodegradation Product 3)	Target chemical 4 (Biodegradation Product 4)
Structure				Unidentified
CAS No.	-	-	787-70-2	-
Chemical name	4,4-biphenyl dimethanol	4'-(hydroxymethyl)-[1,1'-biphenyl]-4-carboxylic acid	biphenyl-4,4'-dicarboxylic acid	-

Case study (Rule B)

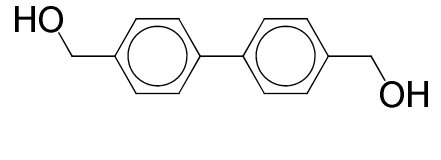
- Relationship between Source Chemical and Target Chemicals -

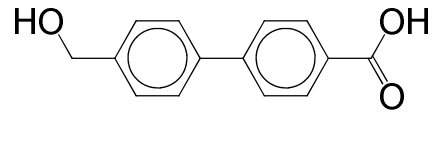
- ✓ Source chemical and target chemicals have the relationship between a parent chemical and its degradation products.
- ✓ It is thought that **structural similarities must be high, because it is assumed that the structure is partially kept during degradation.**

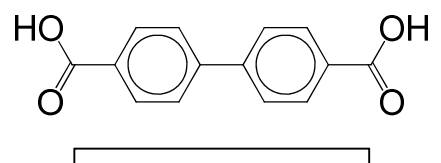
	Source chemical (Parent chemical)
Structure	
logPow Exp.	
logPow Pred. value	
BCF (Exp. value)	High conc. (10 μl): BCF = ≤5 Low conc. (1 μl): BCF = ≤48

"not highly bioaccumulative"

Target chemicals (Degradation products)







Unidentified

Case study (Rule B)
- The result of a polarity comparison -

- ✓ The result of a polarity comparison of source chemical with target chemical (obtained by reverse-phase HPLC) show that **target chemicals are more hydrophilic than source chemical.**
- ✓ The bioaccumulation potential of target chemicals can be judged **"not highly bioaccumulative"** under the CSCL.

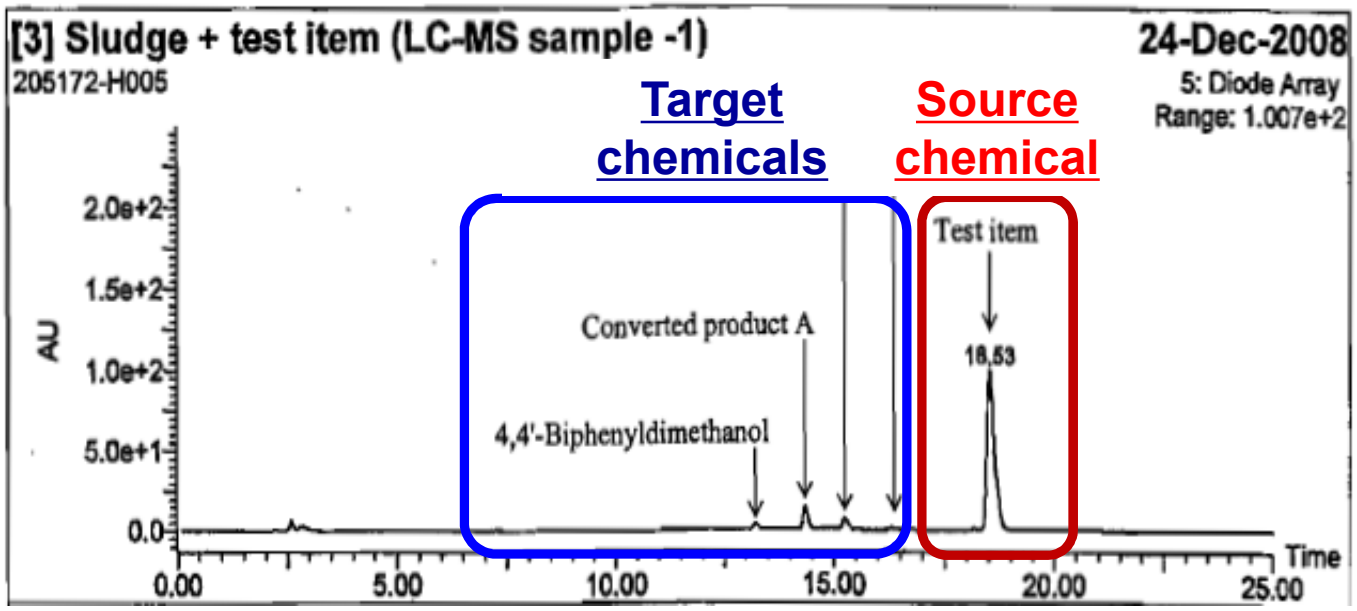


Fig. The test results of a hydrophilic comparison between parent chemical and degradation products by reverse-phase HPLC.

2.2 LOG D < 2.5 (IN CASE OF THE IONIC SUBSTANCE ONLY)

Background

- ✓ If log P is <3.5, that substance is assessed to be “not highly bioaccumulative”.
- ✓ Ionic substances are known as “not highly bioaccumulative” in general (detail information see page 24 and 25).
- ✓ However, the bioaccumulation assessment for an ionic substance is measured by animal testing, because measuring its logP in neutral form is difficult.
- ✓ Therefore, in order to simplify bioaccumulation assessment of ionic substances, a new guidance to use log D (the partition coefficient determined around a pH of 7) was made by METI in June, 2014.

Analysis of the bioaccumulation potential of ionic substances under the CSCL

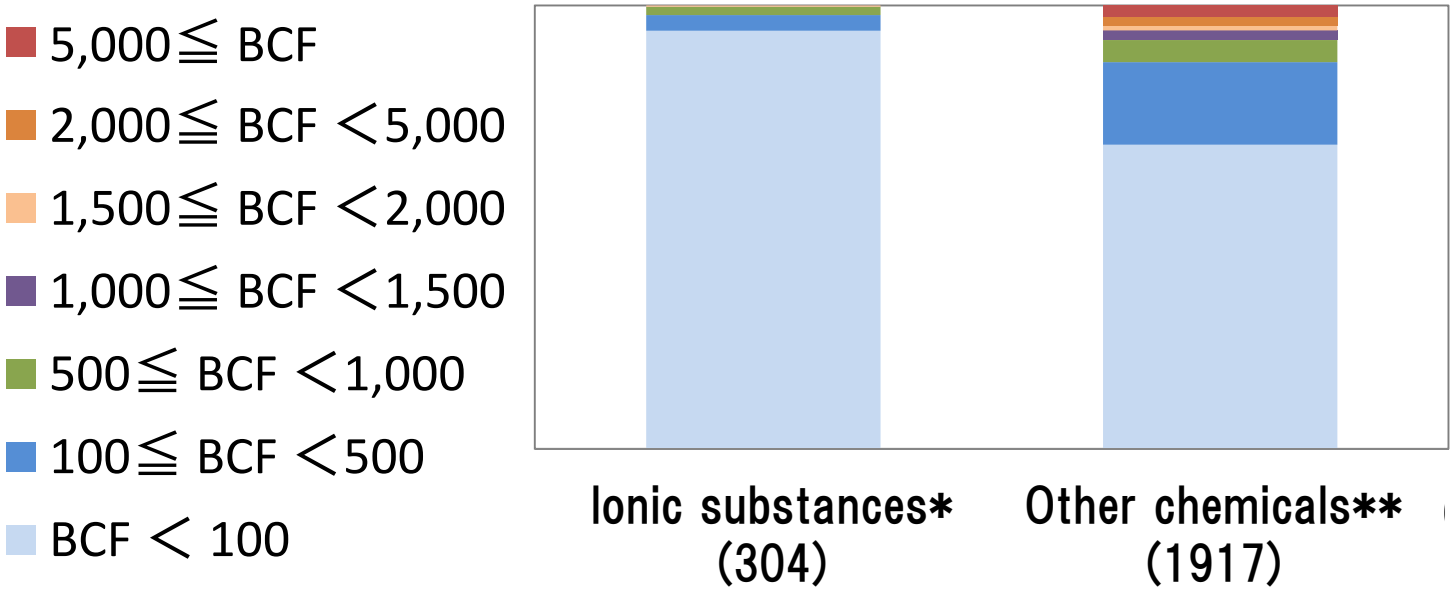
<Analysis detail>

- ✓ 818 existing chemicals and 1411 new chemicals assessed previously from 1975 to October 2012 under the CSCL were listed.
- ✓ NITE made a comparison of BCF value between ionic substances * and other chemicals**.

* ionic substances : carboxylic acid, sulfonic acid and its metal salt(except 8 perfluoro acids), quaternary amine and zwitterion.

** Other chemicals: Substances except ionic substances and perfluoro acid.

Result of data analysis



Measured BCF	Number of Ionic substance* (rate)	Number of other chemicals** (rate)
BCF ＜ 100	286 (94.2%)	1,310 (68.5%)
100≦ BCF ＜500	11 (3.5%)	359 (18.6%)
500≦ BCF ＜1,000	6 (1.9%)	97 (5%)
1,000≦ BCF ＜1,500	0 (0%)	43 (2.2%)
1,500≦ BCF ＜2,000	1 (0.3%)	19 (1%)
2,000≦ BCF ＜5,000	0 (0%)	39 (2%)
5,000≦ BCF	0 (0%)	50 (2.6%)
合計	**304 (100%)**	**1,917 (100%)**

286 out of 304 ionic substances were < BCF 100. (approximately 94 %)

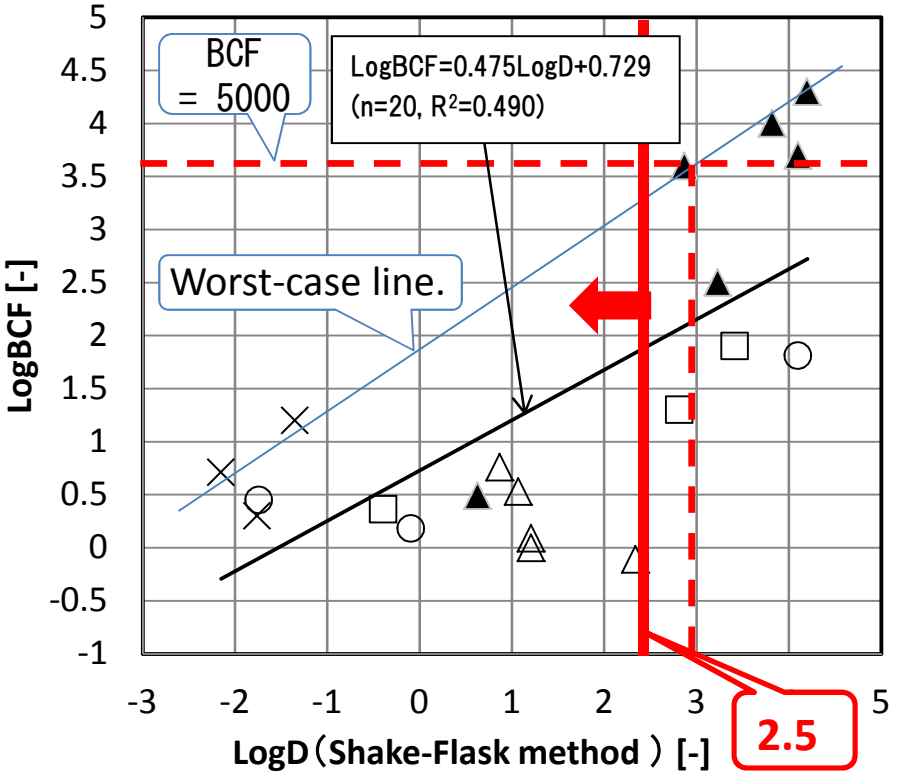
* ionic substances：carboxylic acid, sulfonic acid and its metal salt(except 8 perfluoro acids), quaternary amine and zwitterion.

** Other chemicals: Substances except ionic substances and perfluoro acid.

logBCF vs. logD plot for ionic substances

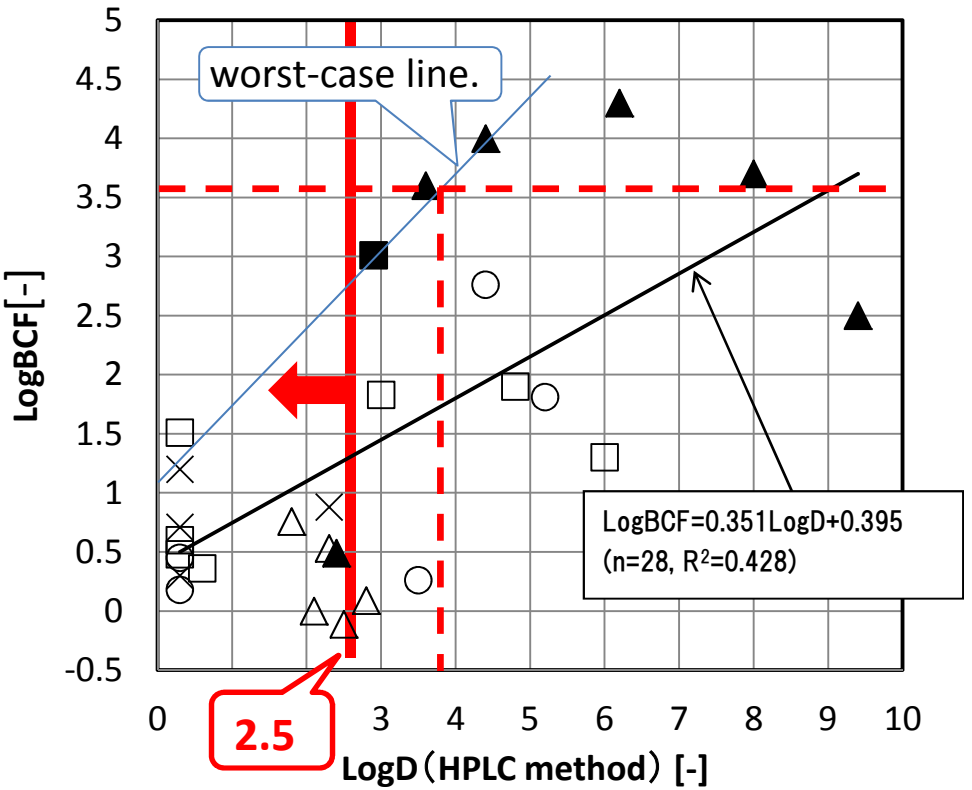
- ✓ In order to study relationship between logBCF and logD (pH=7), we measured LogD of ionic substances, whose measured BCF value is available.
- ✓ Measuring methods are Shake-Flask method (20 substances) and HPLC method (28 substances).

LogD(Shake-Flask method) vs LogBCF



△: carboxylic acid (5), □: sulfonic acid (3), ×: zwitterion (3), ○: quaternary amine (3), ▲: perfluoro carboxylic acid (6)

LogD(HPLC method) vs LogBCF

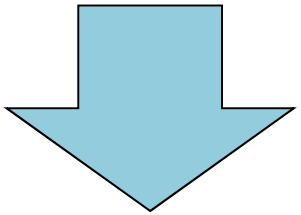


△: carboxylic acid (5), □: sulfonic acid (7), ×: zwitterion (4), ○: quaternary amine (5), ▲: perfluoro carboxylic acid (6), ■: perfluoro sulfonic acid (1)

Conclusion

- Bioaccumulation assessment of ionic substances using logD -

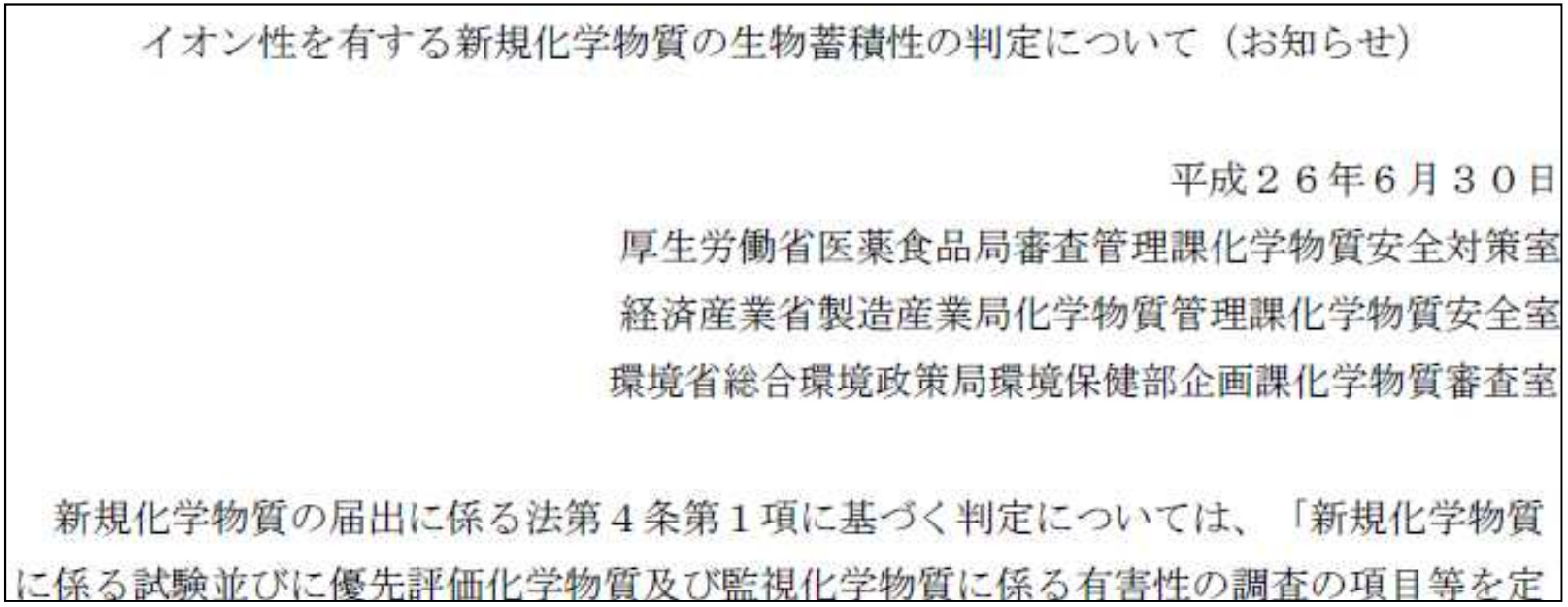
- ✓ Most ionic substances are “not highly bioaccumulative” under the CSCL.
- ✓ There was the weak correlation between log BCF and Log D of ionic substances.



The bioaccumulation potential of ionic substances is possible to assess by using criterion value (Log D < 2.5).

The judgement rule for the bioaccumulation assessment of ionic substances was announced in June 2014.

Ministry of Economy, Trade and Industry in Japan (METI) announced **a new guidance of the bioaccumulation assessment by using logD.**



イオン性を有する新規化学物質の生物蓄積性の判定について（お知らせ）

平成２６年６月３０日

厚生労働省医薬食品局審査管理課化学物質安全対策室

経済産業省製造産業局化学物質管理課化学物質安全室

環境省総合環境政策局環境保健部企画課化学物質審査室

新規化学物質の届出に係る法第４条第１項に基づく判定については、「新規化学物質に係る試験並びに優先評価化学物質及び監視化学物質に係る有害性の調査の項目等を定

※Japanese Only

http://www.meti.go.jp/policy/chemical_management/kasinhou/files/todoke/shinki/140630_logD.pdf

Detail information of the judgement rule

- ✓ If LogD of an ionic compound (e.g. sulfonic acids, carbonic acids, zwitterionic substances, quaternary amines, etc.) is < 2.5, that chemical substance can be assessed to be "not highly bioaccumulative".
- ✓ This method can not apply to any compounds which partially includes trifluoromethyl (CF3-) or tetrafluoroethylene (-CF2-CF2-) structure in their structure.

※Under this method, "an ionic compound which is difficult to measure log P in undissociated state" means, in principle, a compound whose pKa is less than 3 for acids and more than 11 for bases.

※This method does not apply to surfactants, mixture which has distribution of molecular weight, organic metallic compound, low purity compound (except for HPLC method) and inorganic compound.

※Prier consultation with METI/NITE is highly recommended.

※Both Shake-Flask method and HPLC method are applicable to measure log D.

The number of chemicals for the bioaccumulation assessment notified

2.1 Bioaccumulative analogy rule

Period	Number of chemicals
Oct. 2012 - Sep. 2013	10
Oct. 2013 - Sep. 2014	27
Oct. 2014 - Sep. 2015	14
Oct. 2015 - Jan. 2016	6

Before announced.

2.2 log D <2.5

Period	Number of chemicals
July 2014 - Mar. 2015	3
Apr. 2015 – Jan. 2016	4

Thank you for your kind attention.