

生分解性/蓄積性に関連した QSARとリードアクロス ・最新動向

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目次

- 分解性QSAR：BIOWIN5、6
- 蓄積性QSAR：BCFBAF
- QSAR Toolboxを用いたBCF予測
- 最新動向：QSAR Assessment Framework

EPI Suiteのメイン画面

The screenshot displays the EPI Suite software interface. At the top, there is a menu bar with options: File, Edit, Functions, Batch Mode, Show Structure, Output, Fugacity, STP, and Help. Below the menu bar is a blue banner with the text "EPI Suite - Welcome Screen".

On the left side, there is a vertical list of program buttons: AOPWIN, KOWWIN, BIOWIN, MPBPVP, WSKOW, WATERNT, HENRYWIN, KOAWIN, KOCWIN, BCFBAF, HYDROWIN, BioHCwin, DERMWIN, ECOSAR, and EPI Links. Above these buttons is the logo of the United States Environmental Protection Agency.

The main area contains several input fields and buttons:

- Buttons: PhysProp, Previous, Get User, Save User, Search CAS, Calculate (with a calculator icon), Clear Input Fields, Draw, and Output (with radio buttons for Full and Summary).
- Input fields: Input CAS #, Input Smiles, Input Chem Name, Name Lookup, Henry LC, Melting Point, Boiling Point, Water Solubility, Vapor Pressure, Log Kow, Water Depth, Wind Velocity, and Current Velocity.
- Units and scales: atm-m³/mole, Celsius, mm Hg, meters, meters/sec.
- Environmental parameters: River and Lake options for Water Depth, Wind Velocity, and Current Velocity.

At the bottom, there is a text box containing the following information:

The Estimation Programs Interface (EPI) Suite™ was developed by the US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in applications such as to quickly screen chemicals for release potential and "bin" chemicals by priority for future work. Estimated values should not be used when experimental (measured) values are available.

EPI Suite™ cannot be used for all chemical substances. The intended application domain is organic chemicals. Inorganic and organometallic chemicals generally are outside the domain.

Important information on the performance, development and application of EPI Suite™ and the individual programs within it can be found under the Help tab. Copyright 2000-2012 United States Environmental Protection Agency for EPI Suite™ and all component programs except BioHCWIN and KOAWIN.

EPI Suiteに搭載されているモデル

The screenshot shows the EPI Suite software interface. The title bar reads 'EPI Suite'. The menu bar includes 'File', 'Edit', 'Functions', 'Batch Mode', 'Show Structure', 'Output', 'Fugacity', 'STP', and 'Help'. The main window title is 'EPI Suite - Welcome Screen'. Below the title bar, there are buttons for 'PhysProp', 'Previous', 'Get User', 'Save User', 'Search CAS', 'Calculate', and 'Clear Input Fields'. On the left side, there is a vertical list of model names: AOPWIN, KOWWIN, BIOWIN, MPBPVP, WSKOW, WATERNT, HENRYWIN, KOAWIN, KOCWIN, BCFBAF, HYDROWIN, BioHCwin, DERMWIN, ECOSAR, and EPI Links. A yellow callout box highlights the following models and their descriptions:

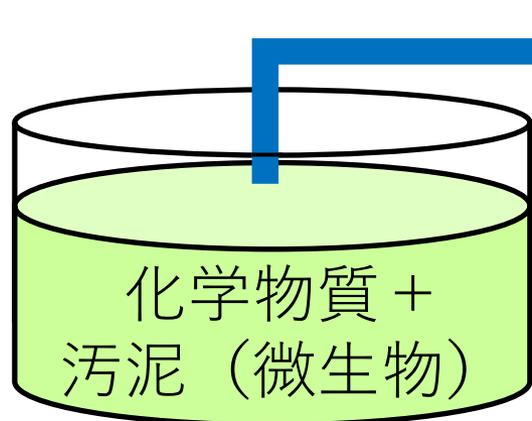
- AOPWIN: 大気中における酸化速度
- KOWWIN: オクタノール-水分配係数
- BIOWIN: 生分解性**
- MPBPVP: 溶解度、沸点、蒸気圧
- WSKOW: 水溶解度
- WATERNT: 水溶解度
- HENRYWIN: ヘンリー一定数
- KOAWIN: オクタノール-空気分配係数
- KOCWIN: 吸着係数
- BCFBAF: 生物濃縮性**
- HYDROWIN: 加水分解反応速度
- BioHCwin: 石油炭化水素の生分解性半減期
- DERMWIN: 皮膚透過速度
- ECOSAR: 水生生物の有害性

At the bottom left, there is a text box: 'The Estimation Program and Toxics and Syracuse chemicals for release (measured) values are... EPI Suite™ cannot be chemicals generally and... Important information found under the Help programs except BioH...'

分解性QSAR：BIOWIN5、6

分解度試験

- ✓ 微生物等による化学物質の分解性を評価するための試験
- ✓ 化審法ではOECD TG 301C/F法の分解度試験結果から評価
- ✓ BOD分解度 < 60% で難分解判定



酸素消費量を測定

試験期間：28日間

$$\text{BOD分解度 (\%)} = \frac{\text{酸素消費量の測定値}}{\text{化学物質が完全に酸化された場合に
必要な理論的酸素要求量}}$$

BIOWINの計算方法

The screenshot displays the EPI Suite software interface. The title bar reads "EPI Suite". The menu bar includes File, Edit, Functions, Batch Mode, Show Structure, Output, Fugacity, STP, and Help. The main window title is "EPI Suite - Welcome Screen". On the left, a vertical list of modules is shown, with "BIOWIN" highlighted in red. The main area contains input fields for "Input CAS #", "Input Smiles:", and "Input Chem Name:". Below these is a "Name Lookup" section with fields for Henry LC, Melting Point, Boiling Point, Water Solubility, Vapor Pressure, and Log Kow. At the bottom, there are fields for "Water Depth", "Wind Velocity", and "Current Velocity", each with sub-fields for "River" and "Lake". A "Calculate" button is visible on the right. The bottom of the window contains a text box with the following information:

The Estimation Programs Interface (EPI) Suite™ was developed by the US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in applications such as to quickly screen chemicals for release potential and "bin" chemicals by priority for future work. Estimated values should not be used when experimental (measured) values are available.

EPI Suite™ cannot be used for all chemical substances. The intended application domain is organic chemicals. Inorganic and organometallic chemicals generally are outside the domain.

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CAS RNによるSMILES入力

①

②

③

④

The Estimation Programs Interface (EPI) Suite™ was developed by the US Environmental Protection Agency and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in a chemicals for release potential and "bin" chemicals by priority for future work. Estimated values should (measured) values are available.

EPI Suite™ cannot be used for all chemical substances. The intended application domain is organic chemicals generally are outside the domain.

Important information on the performance, development and application of EPI Suite™ and the individual found under the Help tab. Copyright 2000-2011 United States Environmental Protection Agency for EPI programs except BioHCWIN and KOAWIN.

Water Depth: meters
Wind Velocity: 5 0.5 meters/sec
Current Velocity: 1 0.05 meters/sec

Enter SMILES: c(cccc1)(c1)Cl
Enter NAME: Benzene, chloro-
NameLookup

構造描画によるSMILES入力

The image illustrates the workflow for entering SMILES via structure drawing in the EPI Suite software. The main window shows the 'BioWin v4.11' interface with the 'DRAW' button highlighted by a red circle (2). On the left sidebar, the 'BIOWIN' button is highlighted by a red circle (1). A '2D Editor' window is open, showing the SMILES string 'c1(C)cccc1' entered in the input field, highlighted by a red circle (3). The chemical structure of chlorobenzene is displayed on the right. A 'BioWin v4.10' dialog box is shown in the foreground, with the 'Calculate' button highlighted by a red circle (5). The dialog box contains the SMILES string 'c(ccc1)(c1)Cl' and the name 'Benzene, chloro-'. A red circle (4) highlights the 'Ok' button in the dialog box. The EPI Suite logo and text are visible in the bottom left corner of the main window.

1. Select BIOWIN from the left sidebar.

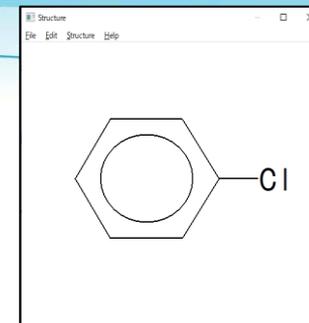
2. Click the DRAW button in the main window.

3. Enter the SMILES string 'c1(C)cccc1' in the 2D Editor window.

4. Click the Ok button in the BioWin v4.10 dialog box.

5. Click the Calculate button in the BioWin v4.10 dialog box.

BIOWIN予測結果



Bio Results

Print Save Results Copy Remove Window Help

SMILES : c1(Cl)ccccc1
CHEM :
MOL FOR: C6 H5 CL1
MOL WT : 112.56

----- BIOWIN v4.10 Results -----

Biowin1 (Linear Model Prediction) : Biodegrades Fast
Biowin2 (Non-Linear Model Prediction): Biodegrades Fast
Biowin3 (Ultimate Biodegradation Timeframe): Weeks
Biowin4 (Primary Biodegradation Timeframe): Days-Weeks
Biowin5 (MITI Linear Model Prediction) : Not Readily Degradable
Biowin6 (MITI Non-Linear Model Prediction): Not Readily Degradable
Biowin7 (Anaerobic Model Prediction): Does Not Biodegrade Fast
Ready Biodegradability Prediction: NO

TYPE	NUM	Biowin1 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic chloride [-CL]	-0.1824	-0.1824
Frag	1	Unsubstituted phenyl group (C6H5-)	0.1281	0.1281
MolWt	*	Molecular Weight Parameter		-0.0536
Const	*	Equation Constant		0.7475
RESULT		Biowin1 (Linear Biodeg Probability)		0.6696

TYPE	NUM	Biowin2 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic chloride [-CL]	-2.0155	-2.0155
Frag	1	Unsubstituted phenyl group (C6H5-)	1.7991	1.7991
MolWt	*	Molecular Weight Parameter		-1.5983

BIOWIN1~7の予測結果が出力される。

BIOWIN1~7の予測結果を算出するのに使用された、部分構造の数と分子量が出力される。

BIOWIN 1～7の違い

	分解性データ		回帰式
	トレーニングセット	予測値	
BIOWIN1	好気性条件下の分解度試験結果に基づくデータ	素早く分解する確率を連続変数で予測、0.5以上であれば素早く分解する	線形回帰式
BIOWIN2			非線形回帰式
BIOWIN3	本質的生分解（無機化するまでの分解）が完了するのに要する時間の専門家による推定値	本質的生分解が完了するのに要する時間を表す	線形回帰式
BIOWIN4	一次生分解性（一段階目の分解）が完了するのに要する時間の専門家による推定値	一次生分解が完了するのに要する時間を表す	線形回帰式
BIOWIN5	OECD 301C試験から得られた良分解性（1）/難分解性（0）のデータ	素早く分解する確率を連続変数で予測、0.5以上であれば良分解性	線形回帰式
BIOWIN6			非線形回帰式
BIOWIN7	嫌気性条件下の分解度試験結果に基づくデータ	素早く分解する確率を連続変数で予測、0.5以上であれば素早く分解する	線形回帰式

生分解性予測モデル（例：BIOWIN5）

42の部分構造及び分子量を記述子とし、下式により予測がなされる。

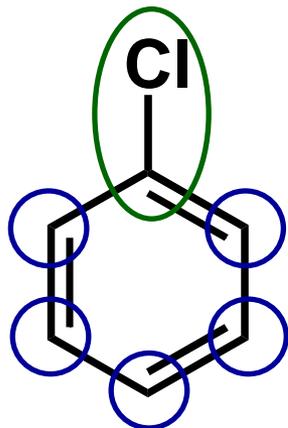
Y_j が0.5以上で易分解性、0.5未満で難分解性と判定される。

$$Y_j = a_0 + a_1 f_1 + a_2 f_2 + \dots + a_n f_n + a_m MW$$

- Y_j : 物質Jが易分解性となる可能性
- f_n : 物質Jの部分構造nの数
- a_n : 部分構造nの回帰係数
- MW : 分子量
- a_m : 分子量の回帰係数
- a_0 : 定数項

分解性に対する各部分構造の寄与を
数値で表現（回帰式モデル）

【クロロベンゼンの予測結果】

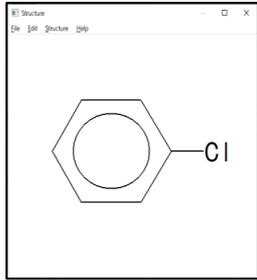


記述子	回帰係数	数量	合計
Ar-Cl	-0.0392	1	-0.0392
Ar-H	0.0004	5	0.0020
MW	-0.00158	113	-0.1775
定数項			0.5544
合計			0.3397

0.5未満なので
難分解予測

BIOWIN5、BIOWIN6の出力結果

- 化審法生分解性試験条件下（OECD301C法）において、BOD分解度が60%以上となる確率を連続変数で予測
- 0.5未満で難分解性予測、0.5以上で良分解性予測
- BIOWIN5では線形回帰式、BIOWIN6では非線形の回帰式により予測



Bio Results				
Print Save Results Copy Remove Window Help				
TYPE	NUM	Biowin5 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic chloride [-CL]	-0.0392	-0.0392
Frag	5	Aromatic-H	0.0004	0.0020
MolWt	*	Molecular Weight Parameter		-0.1775
Const	*	Equation Constant		0.5544
RESULT Biowin5 (MITI Linear Biodeg Probability)				0.3397
TYPE	NUM	Biowin6 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic chloride [-CL]	-0.7609	-0.7609
Frag	5	Aromatic-H	0.0342	0.1709
MolWt	*	Molecular Weight Parameter		-1.9473
RESULT Biowin6 (MITI Non-Linear Biodeg Probability)				0.2942

A Probability Greater Than or Equal to 0.5 indicates --> Readily Degradable
A Probability Less Than 0.5 indicates --> NOT Readily Degradable

BIOWIN5
(0.5未満なので
難分解性予測)

BIOWIN6
(0.5未満なので
難分解性予測)

BIOWIN5、BIOWIN6出力結果の信頼性 (適用範囲)

7.3.2. Model Domain

The Table below lists, for each fragment, the maximum number of instances of that fragment in any of the 589 original training set compounds and in the update 960 compound training set of 2017 (the minimum number of instances is zero, since not all compounds had every fragment). The minimum molecular weight for both data sets is 30 (formaldehyde) and the maximums are 959 (original data set) and 1215 (update). Currently there is no universally accepted definition of model domain. However, users may wish to consider the possibility that biodegradability estimates are less accurate for compounds outside the MW range of the training set compounds, and/or that have more instances of a given fragment than the maximum for all training set compounds. It is also possible that a compound may have a functional group(s) or other structural features not represented in the training set, and for which no fragment coefficient was developed; and that a compound has none of the fragments in the model's fragment library. In the latter case, predictions are based on molecular weight alone. These points should be taken into consideration when interpreting model results.

Fragment or parameter	BIOWIN5 and BIOWIN6, v4.10 (Tunkel et al. 2000)			BIOWIN5 and BIOWIN6 Updates (v4.11)		
	Linear coefficient	Nonlinear coefficient	Frequency ^a	Linear coefficient	Nonlinear coefficient	Frequency ^a
Equation constant	0.712	2.526	-	0.554374	1.66229	-
Aldehyde	0.411	2.744	14	0.2323	0.91841	23
Aliphatic acid	0.181	1.135	22	0.3161	2.0894	59
Aliphatic alcohol	0.161	1.004	74	0.1359	0.71447	125
Aliphatic amine	0.033	-0.284	18	-0.01667	-0.46545	43
Aliphatic bromide	0.097	-0.556	13	0.01746	-0.91472	18
Aliphatic chloride	0.001	-0.639	46	0.01743	-0.63918	58
Aliphatic ether	0.001	-0.107	35	-0.01056	-0.202	67
Amide	0.127	0.886	24	0.02975	0.0424	44
Aromatic acid	0.377	2.445	25	0.3443	2.14031	28
Aromatic alcohol	0.064	0.488	65	0.03823	0.27234	106
Aromatic amine	-0.158	-1.226	55	-0.1273	-1.31698	83
Aromatic bromide	0.167	1.502	11	0.07182	0.60948	14
Aromatic chloride	0.006	-0.219	55	-0.03917	-0.7609	83
Aromatic ether	0.195	1.323	32	0.08089	0.51834	57
Aromatic iodide	-0.384	-12.522	1	-0.5092	-19.21483	1
Aromatic nitro	-0.188	-2.403	33	-0.1901	-2.73231	51
Azo group	-0.046	-10.613	2	0.1165	-12.86945	11
Carbamate	-0.043	0.419	6	-0.1968	-1.17024	8

予測対象物質の分子量、部分構造の数が、トレーニングセットの範囲に収まらない場合は、予測結果の信頼性が比較的低くなると考えられる。

BIOWIN5、BIOWIN6出力結果の信頼性 (バリデーション結果)

【BIOWIN5、6 (ver.4.11) の正答率】

	パラメーター	BIOWIN 5	BIOWIN 6
トレーニング セットによる検証	難分解性	494/575 (85.9%)	490/575 (85.2%)
	良難分解性	275/385 (71.4%)	300/385 (77.9%)
	合計	769/960 (80.1%)	790/960 (82.3%)
バリデーション セットによる検証	難分解性	253/292 (86.6%)	253/292 (86.6%)
	良難分解性	128/185 (69.2%)	147/185 (79.5%)
	合計	381/477 (79.8%)	400/4877 (83.7%)

BIOWIN5、6どちらのモデルでも、おおむね70%以上の予測精度

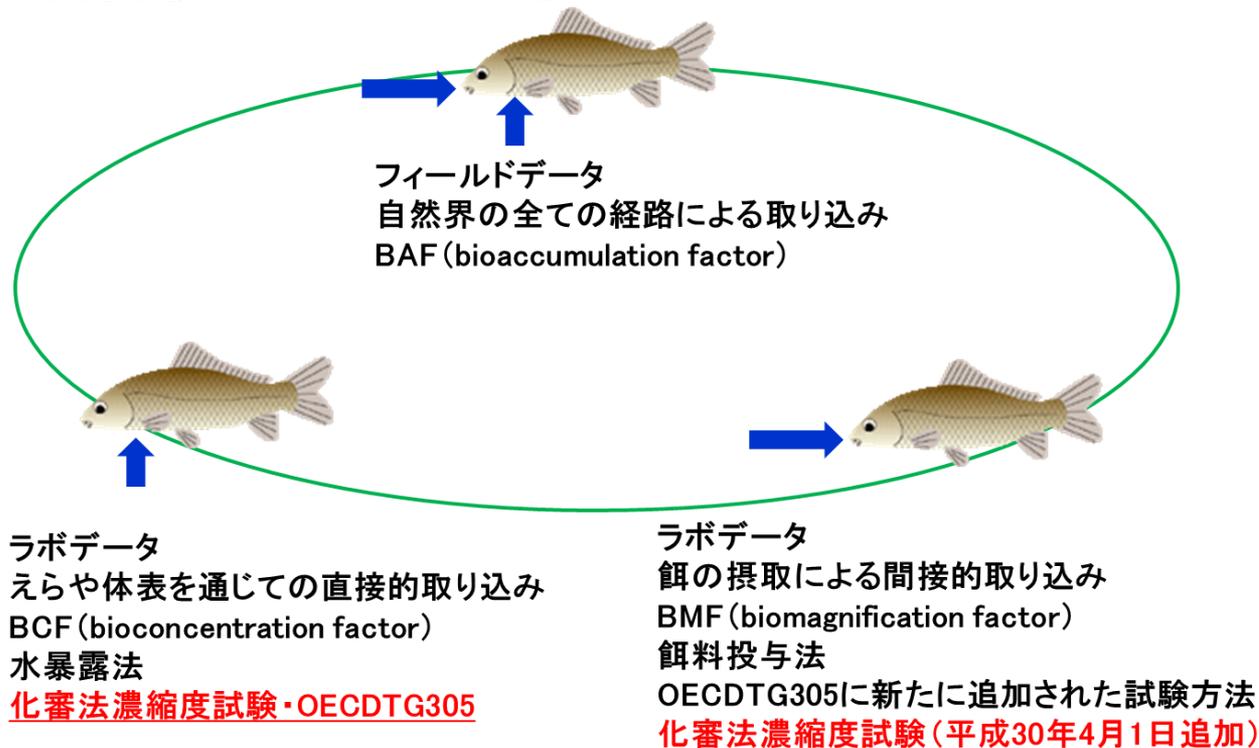
蓄積性QSAR : BCFBAF

濃縮度試験

化審法では、濃縮度試験の結果から生物蓄積性を評価

濃縮度試験の概要

生物蓄積性に係る知見



NIET講座資料 III.サステイナブルな化学物質管理の推進に向けて

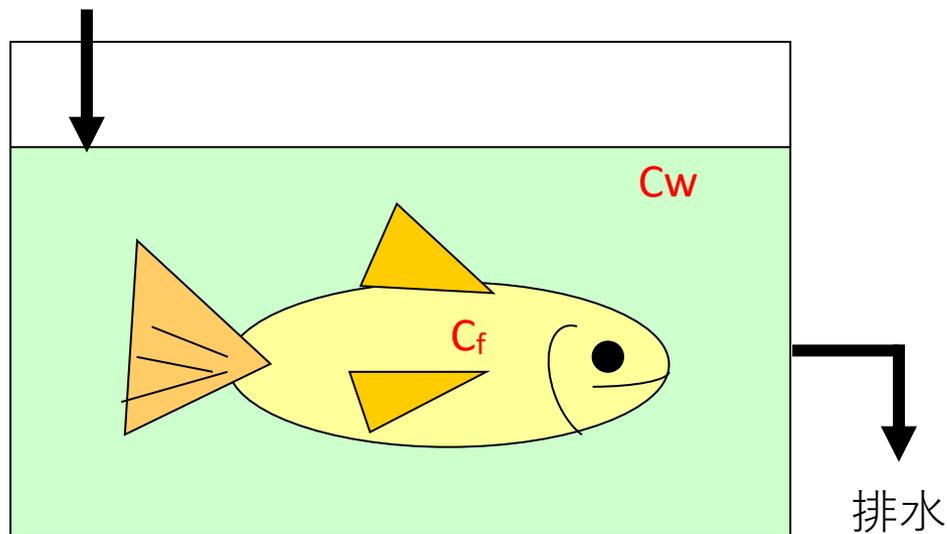
1.化審法における新規化学物質の届出対象と申請資料のポイント及び分解・蓄積性試験と判定の概論

(<https://www.nite.go.jp/data/000141567.pdf>)

水暴露法

BCF=5,000L/kgが高蓄積性の判定基準

試験水（水、化学物質、酸素etc.）



化審法の試験法（OECD TG 305）

方式：流水式、2濃度区（または1濃度区）

魚種：コイ（主に）

試験温度： $25 \pm 2^\circ\text{C}$

暴露期間：28日間（主に）

生物濃縮係数（BCF） = C_f / C_w

C_f : 平衡時の魚体中の化学物質濃度

C_w : 平衡時の水中の化学物質濃度

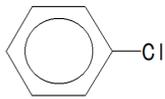
BCFBAFの計算方法

The screenshot displays the EPI Suite software interface. The title bar reads "EPI Suite". The menu bar includes File, Edit, Functions, Batch Mode, Show Structure, Output, Fugacity, STP, and Help. The main window title is "EPI Suite - Welcome Screen". On the left, a vertical list of program buttons is shown, with "BCFBAF" highlighted by a red rectangle. The main area contains input fields for "Input CAS #", "Input Smiles:", and "Input Chem Name:". Below these is a "Name Lookup" section with fields for Henry LC, Melting Point, Boiling Point, Water Solubility, Vapor Pressure, and Log Kow. A table for environmental parameters is also present:

	River	Lake	
Water Depth:	1	1	meters
Wind Velocity:	5	0.5	meters/sec
Current Velocity:	1	0.05	meters/sec

At the bottom, a text box provides information about the software: "The Estimation Programs Interface (EPI) Suite™ was developed by the US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in applications such as to quickly screen chemicals for release potential and "bin" chemicals by priority for future work. Estimated values should not be used when experimental (measured) values are available. EPI Suite™ cannot be used for all chemical substances. The intended application domain is organic chemicals. Inorganic and organometallic chemicals generally are outside the domain. Important information on the performance, development and application of EPI Suite™ and the individual programs within it can be found under the Help tab. Copyright 2000-2012 United States Environmental Protection Agency for EPI Suite™ and all component programs except BioHCWIN and KOAWIN."

BCFBAFの予測結果



生体内分解予測結果
(部分構造の数と
logKow、分子量)

BCFBAF Results

Print Save Results Copy Remove Window Help

SMILES : c1(Cl)cccc1
CHEM :
MOL FOR: C6 H5 CL1
MOL WT : 112.56

----- BCFBAF v3.01 -----

Summary Results:
Log BCF (regression-based estimate) : 1.541 (BCF = 34.74 L/kg wet-wt)
Biotransformation Half-Life (days) : -1.019 (Bio Half-life = 0.0957 days)
Log BAF (Arnot-Gobas upper trophic): 1.40 (BAF = 25 L/kg wet-wt)

Experimental BCF-kM Database Structure Match:

Name : Benzene, chloro-
CAS Num : 000108-90-7
Log BCF : 1.25 (BCF = 17.8 L/kg wet-wt)
BCF Data : BCF NonIonic Training Set
Log Bio HL: -1.019 (Bio Half-life = 0.0957 days)
Bio Data : kM Training Set

BCF (Bioconcentration Factor):

Log Kow (estimated) : 2.64
Log Kow (experimental): 2.84
Log Kow used by BCF estimates: 2.84

Equation Used to Make BCF estimate:
Log BCF = 0.6598 log Kow - 0.333 + Correction

Correction(s): Value
No Applicable Correction Factors

Estimated Log BCF = 1.541 (BCF = 34.74 L/kg wet-wt)

実測値情報

回帰式によるBCF予測結果
(logKowによる回帰式と補正係数)

BCFBAF Results

Print Save Results Copy Remove Window Help

Whole Body Primary Biotransformation Rate

TYPE	NUM	LOG BIOTRANSFORMATION FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic chloride [-CL]	0.3778	0.3778
Frag	1	Unsubstituted phenyl group (C6H5-)	-0.6032	-0.6032
Frag	5	Aromatic-H	0.2664	1.3319
Frag	1	Benzene	-0.4277	-0.4277
L Kow	*	Log Kow = 2.84 (experimental)	0.3073	0.8729
MolWt	*	Molecular Weight Parameter		-0.2886
Const	*	Equation Constant		-1.5371
RESULT		LOG Bio Half-Life (days)		-0.2740
RESULT		Bio Half-Life (days)		0.532
NOTE		Bio Half-Life Normalized to 10 g fish at 15 deg C		

Biotransformation Rate Constant:
kM (Rate Constant): 1.303 /day (10 gram fish)
kM (Rate Constant): 0.7326 /day (100 gram fish)
kM (Rate Constant): 0.412 /day (1 kg fish)
kM (Rate Constant): 0.2317 /day (10 kg fish)

Note: For Arnot-Gobas BCF & BAF Methods, Experimental Km Half-Life Used:
Exp Km Half-Life = -1.019 days (Rate Constant = 7.241/ day)

Arnot-Gobas BCF & BAF Methods (including biotransformation rate estimates):
Estimated Log BCF (upper trophic) = 1.398 (BCF = 25 L/kg wet-wt)
Estimated Log BAF (upper trophic) = 1.398 (BAF = 25 L/kg wet-wt)
Estimated Log BCF (mid trophic) = 1.399 (BCF = 25.05 L/kg wet-wt)
Estimated Log BAF (mid trophic) = 1.399 (BAF = 25.05 L/kg wet-wt)
Estimated Log BCF (lower trophic) = 1.387 (BCF = 24.39 L/kg wet-wt)
Estimated Log BAF (lower trophic) = 1.388 (BAF = 24.41 L/kg wet-wt)

Arnot-Gobas BCF & BAF Methods (assuming a biotransformation rate of zero):
Estimated Log BCF (upper trophic) = 1.873 (BCF = 74.72 L/kg wet-wt)
Estimated Log BAF (upper trophic) = 1.915 (BAF = 82.14 L/kg wet-wt)

Arnot-Gobasモデルによる
BCFとBAF予測結果

BCFBAF回帰式（非イオン性物質） 予測方法

非イオン性物質

1. 化学構造からlogKowを推計（またはlogKow（実測値）を入力）
2. logKowに応じた計算方法で予測
 - A) $\log Kow < 1$ 定数値による予測（BCF=3.2）
 - B) $1 \leq \log Kow \leq 7$ 予測式（1）を用いる
 - C) $7 < \log Kow$ 予測式（2）を用いる

$$\text{Log BCF} = 0.6598 \text{ Log Kow} - 0.333 + \sum \text{correction factors} \quad \text{式（1）}$$

(n = 396, $r^2 = 0.792$, $Q^2 = 0.78$, std dev = 0.511, avg dev = 0.395)

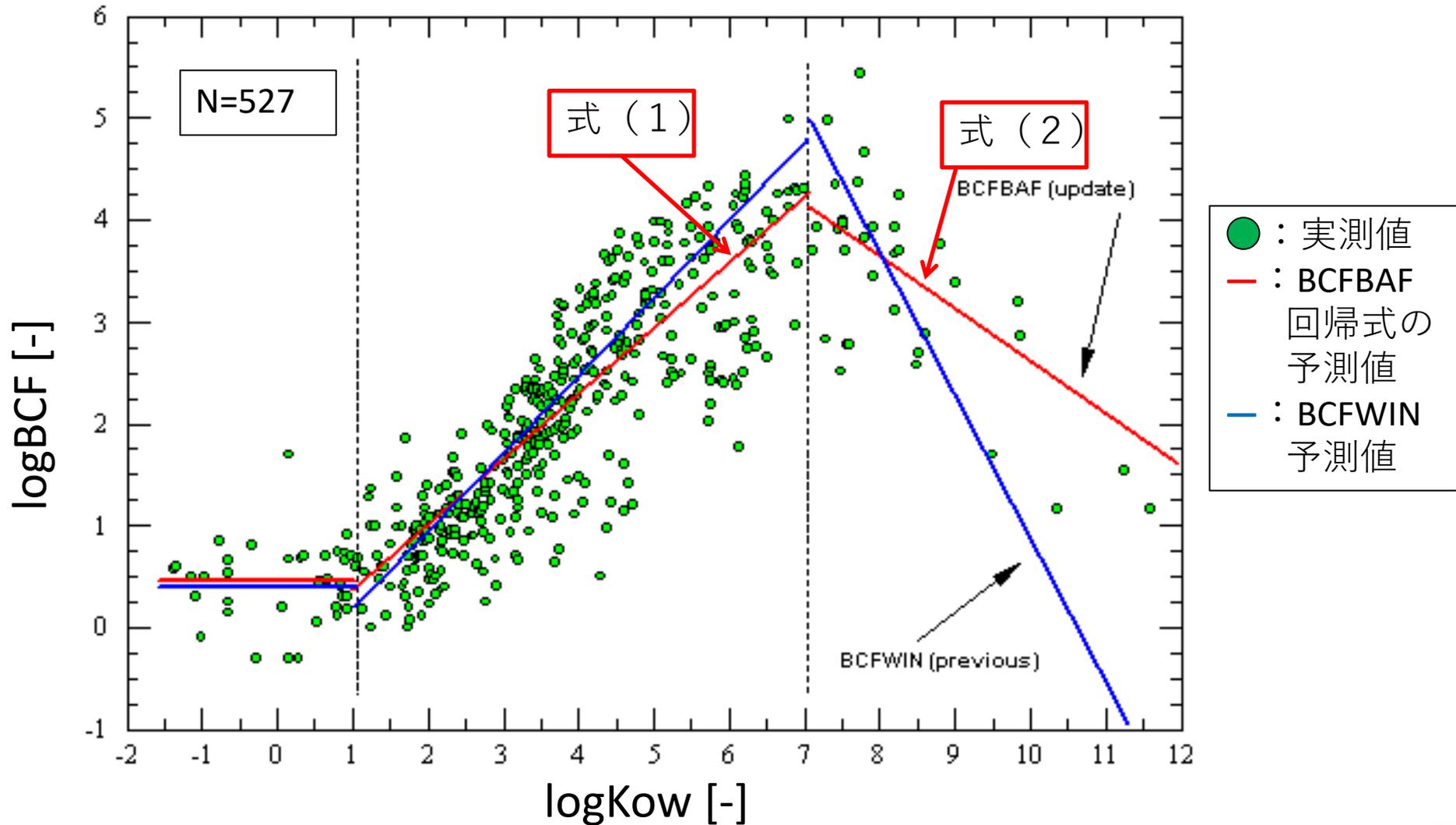
$$\text{Log BCF} = -0.49 \text{ Log Kow} + 7.554 + \sum \text{correction factors} \quad \text{式（2）}$$

(n = 35, $r^2 = 0.634$, $Q^2 = 0.57$, std dev = 0.538, avg dev = 0.396)

※Correction factors： 各骨格及び官能基毎の補正係数

BCFBAF回帰式（非イオン性物質）

予測結果と実測値



BCFBAF回帰式（イオン性物質） 予測方法

イオン性物質

1. 化学構造からlogKowを推計（またはlogKow（実測値）を入力）
2. logKowに応じて定性値による予測

logKow ≤ 5 logBCF=0.5 (BCF=3.2)

5 < logKow ≤ 6 logBCF=1.0 (BCF=10)

6 < logKow ≤ 8 logBCF=1.75 (BCF=56.2)

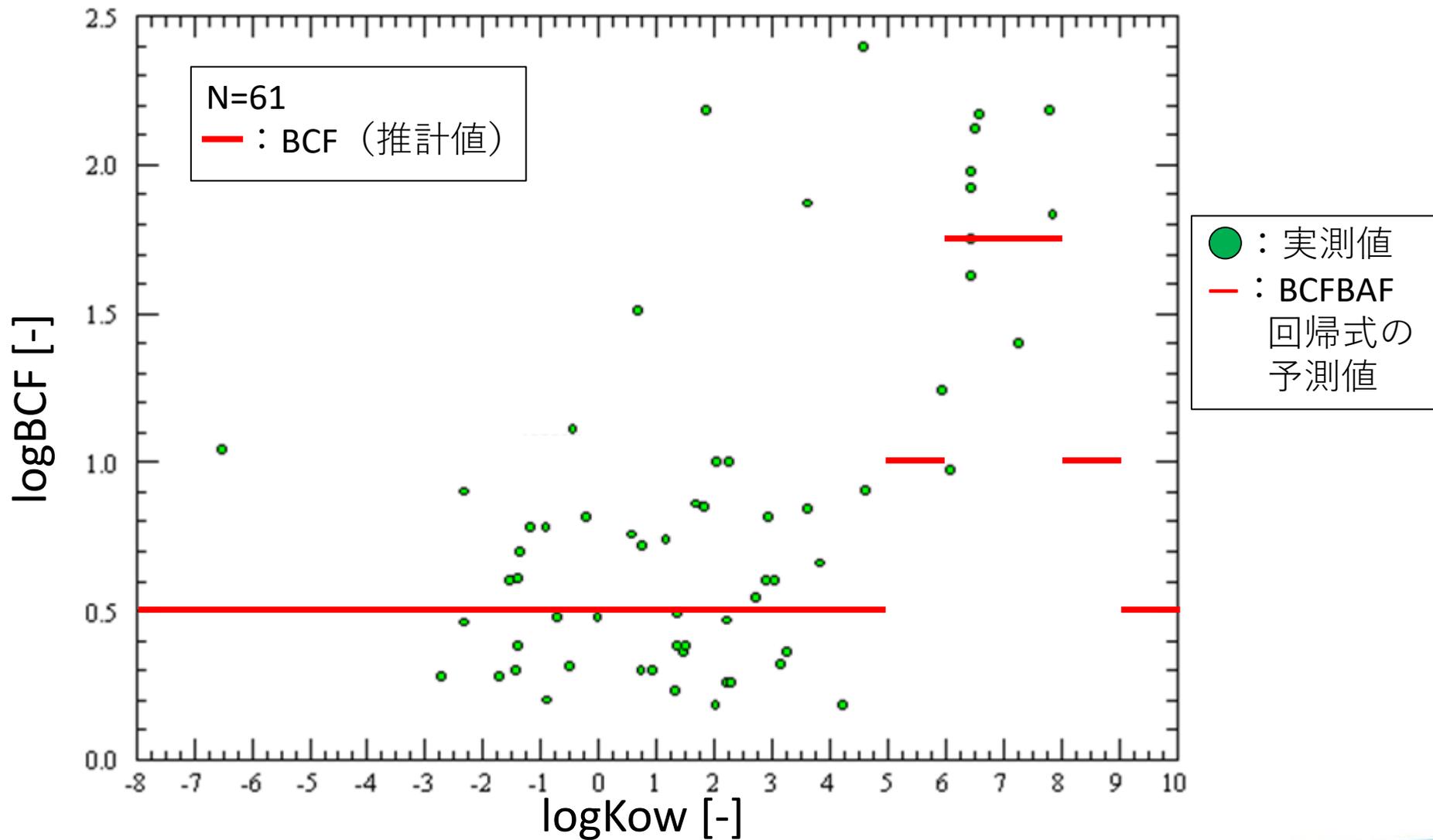
8 < logKow ≤ 9 logBCF=1.0 (BCF=10)

9 < logKow logBCF=0.5 (BCF=3.2)

原著論文
(logBCF=0.75) から更新されている。

BCFBAF回帰式（イオン性物質）

予測結果と実測値



BCFBFAF回帰式

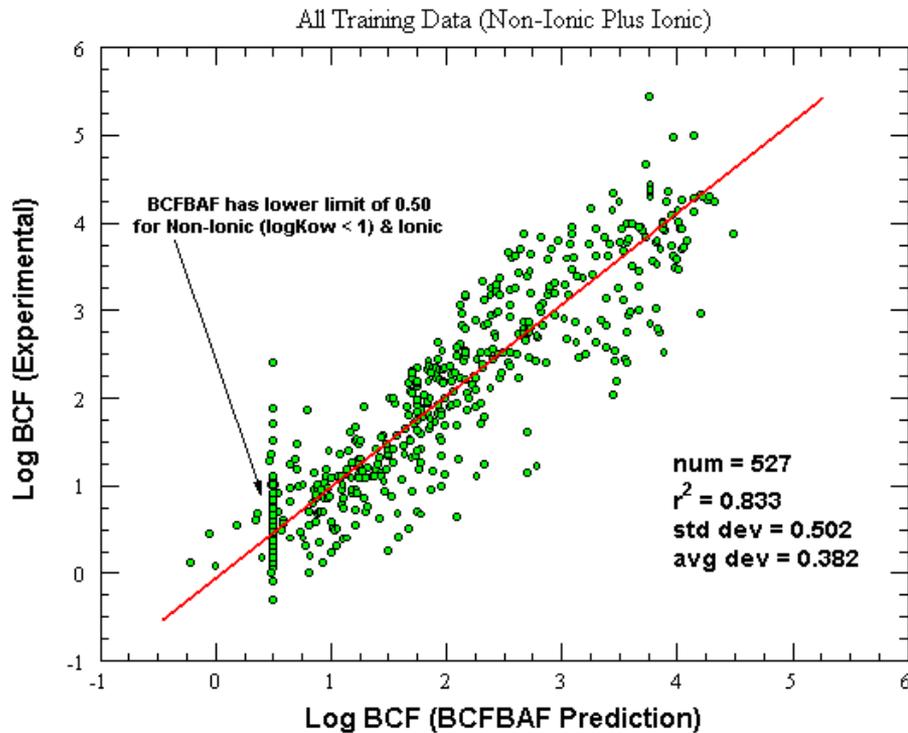
予測結果の信頼性（適用範囲）

The screenshot displays the BCFBAF software interface. On the left, a navigation tree lists various sections, with 'Bioconcentration (BCF)' and 'Appendix E' highlighted with red boxes. The central window shows a scatter plot of Log BC (y-axis) versus Log BCF (BCFBFAF) (x-axis), with a red regression line and green data points. Below the plot, the text '7.1.3. Estimation Domain' is visible. The right window, titled 'Appendix E. BCF Non-Ionic Correction Factors Used by BCFBAF', contains a table of correction factors. The table has five columns: Correction Factor, BCFBAF New Coef, BCFWIN Old Coef, No. Compounds containing Factor in Training set, and Maximum Number of each Factor in any Individual compound. The table lists various chemical groups and their corresponding coefficients and counts.

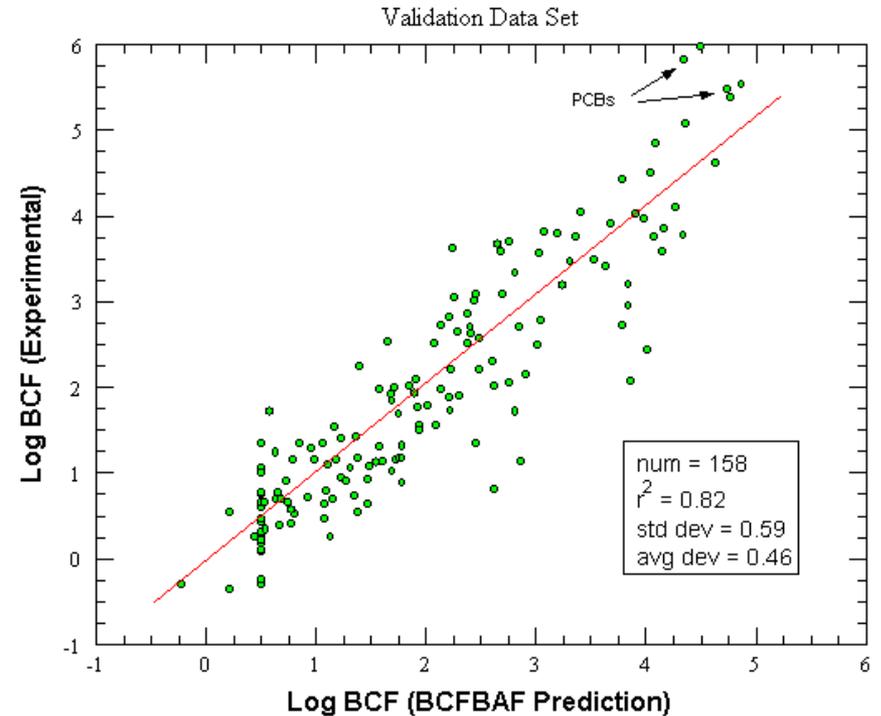
Correction Factor	BCFBFAF New Coef	BCFWIN Old Coef	No. Compounds containing Factor in Training set	Maximum Number of each Factor in any Individual compound
Ketone (aromatic connection)	-0.5851	-0.84	12	1
Phosphate ester	-0.8250	-0.78	14	1
Multi-halogenated biphenyl/PAH	0.5860	0.62	13	1
Aromatic ring-CH-OH	-0.2556	-0.65	5	1
Aromatic sym-triazine ring	-0.5169	-0.32	2	1
Tert-Butyl ortho-phenol type	-0.2220	-0.45	8	1
Phenanthrene ring	0.6609	0.48	2	1
Cyclopropyl-C(=O)-O- ester	-1.2591	-1.65	3	1
Alkyl chains (8+ CH2 groups) log Kow >4 < 7.0	-1.3743	-1.00	2	1
Alkyl chains (8+ CH2 groups) log Kow 7-10	-0.5965	-1.50	2	1
Disulfide (-S-S-) ** NEW Descriptor	-1.3404	---	2	1
Multi-halogenated phenol **NOT Used BCFBAF	---	-0.40		

予測対象物質の分子量やlog Kow、補正係数の出現数、部分構造の数がトレーニングセットの範囲に収まらない場合は、予測結果の信頼性が比較的低くなると考えられる。

BCFBAF回帰式予測結果の信頼性 (バリデーション結果)



トレーニングセットによる検証



バリデーションセットによる検証

生体内分解速度予測方法

1. 化学構造からlogKowを推計（またはlogKow（実測値）を入力）

$$\text{Log } kM/\text{Half-Life (in days)} = 0.30734215 * \text{LogKow} - 0.0025643319 * \text{MolWt} - 1.53706847 + \sum(F_i * n_i)$$

kM : 生体内分解速度定数

Half-life : 生体内分解半減期

MolWt : 分子量

$\sum(F_i * n_i)$: 各骨格及び官能基毎の補正係数とそれらの数の積分の合計

生体内分解速度予測結果の信頼性 (適用範囲)

7.2.3. Estimation Domain

Appendix F gives for each fragment the maximum number of instances of that fragment number of instances is of course zero, since not all compounds had every fragment logKow are listed below. Currently there is no universally accepted definition of what that biotransformation estimates are less accurate for compounds outside the MW have more instances of a given fragment than the maximum for all training set comp functional group(s) or other structural features not represented in the training set, a compound has none of the fragments in the model's fragment library. These points results.

Training Set (421 Compounds):

Molecular Weight:
Minimum MW: 68.08 (Furan)
Maximum MW: 959.17 (Decabromodiphenyl ether)
Average MW: 259.75

Log Kow:
Minimum LogKow: 0.31 (Benzenesulfonamide)
Maximum LogKow: 8.70 (Decabromodiphenyl ether)

Uncertainty in the model predictions must be considered for model applications. The develop the model is about 5.5. A confidence factor of 5.5 suggests that 95% of the between 5.5 x k_M and $k_M/5.5$ assuming a log normal distribution. This degree of uncertainty in the distribution. The log MAE from the test set corresponds to a confidence distribution and could also provide screening level guidance for the expected range uncertainty (1.5 - 1.7 orders of magnitude) is also generally consistent with present variability (Annot et al., 2008a).

The model contains a large set of unique structural fragments so that it can be broad fragments do not reflect the entire domain of possible structural fragments for organic results for all chemicals in all fish species and it is difficult to define precisely the domain of biotransformation rates for substances that have molecular components that significant in model development. The database used to develop the model did not include many larger molecules (molar mass >600); therefore, the model may not accurately predict model did not include metals or organometals, pigments or dyes, or perfluorinated substances.

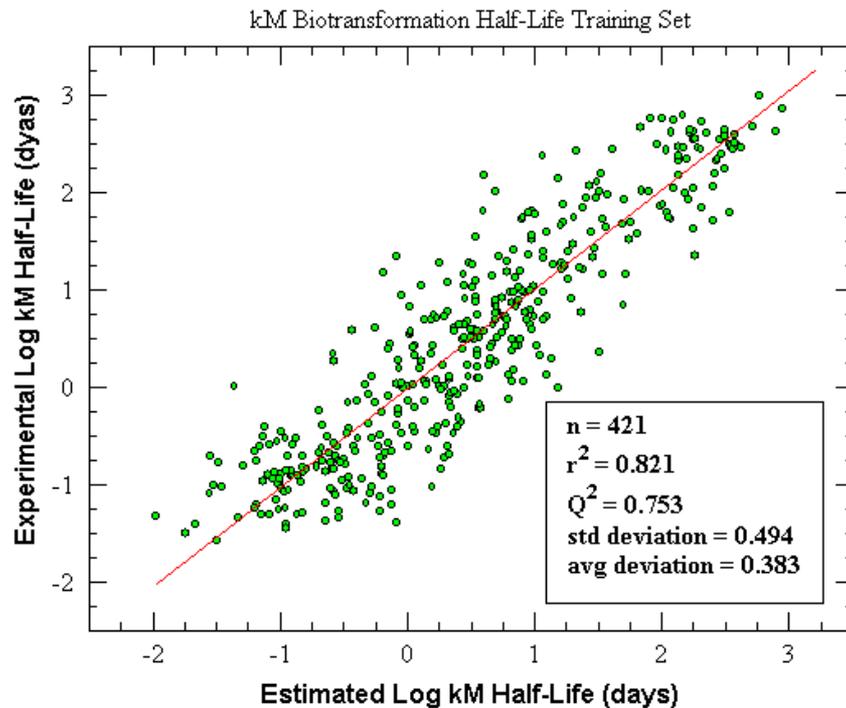
Appendix F
km Biotransformation Fragments & Coefficient Values

The Training Set used to derive the Coefficient Values listed below contained a total of 421 compounds (see Appendix I for the compound list)

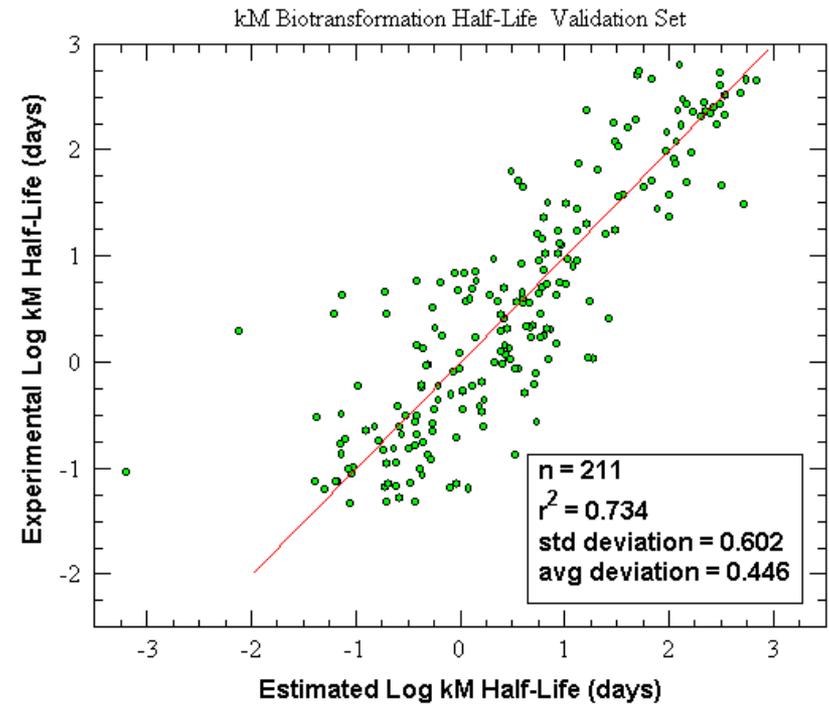
Fragment Description	Coefficient Value	No. Compounds containing fragment in Total Training Set	Maximum Number of each fragment in any Individual compound
Nitroso [-N-N=O]	-0.42851048	1	1
Linear C4 terminal chain [CCC-CH3]	0.03412373	43	3
Aliphatic alcohol [-OH]	-0.06155701	7	3
Aromatic alcohol [-OH]	-0.47273947	26	2
Aliphatic acid [-C(=O)-OH]	0.38030117	1	2
Aldehyde [-CHO]	0.24648749	1	1
Ester [-C(=O)-O-C]	-0.76052851	15	2
Amide [-C(=O)-N or -C(=S)-N]	-0.59521049	5	2
Triazine ring (symmetric)	-0.01226285	2	1
Aliphatic chloride [-Cl]	0.36076089	36	12
Aromatic chloride [-Cl]	0.37784643	145	10
Aliphatic bromide [-Br]	0.27340813	7	6
Aromatic bromide [-Br]	0.39635369	21	10
Aromatic iodide [-I]	0.21395406	1	1
Carbon with 4 single bonds & no hydrogens	-0.29842827	47	10
Aromatic nitro [-NO2]	-0.02177166	33	2
Aliphatic amine [-NH2 or -NH-]	0.40673985	1	1
Aromatic amine [-NH2 or -NH-]	-0.28895783	31	2
Cyanide / Nitriles [-C#N]	0.1542211	8	2
Sulfonic acid / salt -> aromatic attach	0.0247512	2	1
Polyaromatic hydrocarbon (4 or more rings)	0.46164904	9	1
Pyridine ring	-0.90212009	3	1
Aromatic ether [-O-aromatic carbon]	-0.06939912	51	5
Aliphatic ether [-C-O-C]	-0.02324019	14	2
Ketone [-C-C(=O)-C]	-0.1800634	10	2
Tertiary amine	-0.78792477	5	7

- トレーニングセットに含まれておらず、生体内変化プロセスに大きな影響を与える部分構造を持つ物質は正しく予測できない場合がある。
- 生理的pHで解離する物質や分子量が600以上の物質は正しく予測できない場合がある。
- 金属、有機金属、顔料、染料、過フッ化化合物には使用されるべきではない。

生体内分解速度予測結果の信頼性 (バリデーション結果)



トレーニングセットによる検証



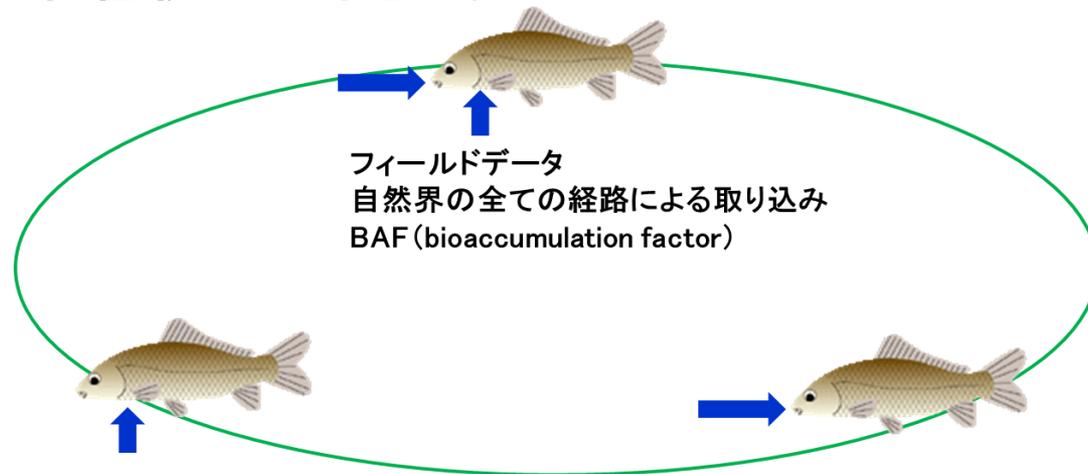
バリデーションセットによる検証

Arnot-Gobasモデル予測方法

1. 化学構造からlogKowを推計（またはlogKow（実測値）を入力）
2. 魚類についての3つの栄養段階（upper, middle, lower）ごとに、次ページに掲載する式で、BCFとBAFを予測

濃縮度試験の概要

生物蓄積性に係る知見



Arnot-Gobasモデル予測方法

$$BCF = (1 - L_B) + \left(\frac{k_1 \cdot \phi}{(k_2 + k_E + k_G + k_M)} \right) \quad BAF = (1 - L_B) + \left(\frac{k_1 \cdot \phi + (k_D \cdot \beta \cdot \tau \cdot L_D \cdot Kow)}{(k_2 + k_E + k_G + k_M)} \right)$$

L_B : 生物中脂質含有率 L_D : 食物連鎖最下位生物中脂質含有率	0.107 (upper), 0.0685 (middle), 0.0598 (lower) 0.01
k_1 : 取込速度定数 k_D : 食餌経路取込速度定数	$k_1 = 1 / ((0.01 + 1/Kow) \cdot w^{0.4})$ $k_D = 0.02 \cdot w^{-0.015} \cdot e^{0.06 \cdot T} / (5 \cdot 10^{-8} \cdot Kow + 2)$ w : 体重 (1.53 (upper), 0.184 (middle), 0.096 (lower)kg) T : 温度 (10 °C)
ϕ : 水中フリー溶存態割合	$\phi = 1 / (1 + \chi_{POC} \cdot 0.35 \cdot Kow + \chi_{DOC} \cdot 0.08 \cdot Kow)$ χ_{POC} : 有機炭素粒子態濃度 (5×10^{-7} g/ml) χ_{DOC} : 有機炭素溶存対濃度 (5×10^{-7} g/ml)
k_2 : 排泄度定数	$k_2 = k_1 / (L_B \cdot Kow)$
k_E : ふん便排出速度定数	$k_E = 0.125 \cdot k_D$
k_G : 成長速度定数	$k_G = 0.000502 \cdot w^{-0.2}$
k_M : 代謝変換速度定数	実測値又はQSAR予測結果
β : 食物網中生物濃縮係数 τ : 食物連鎖最大希釈率 (食物網中生物の代謝能を表す)	62.7 (upper), 30.1 (middle), 16.1 (lower) $\tau = (0.0065 / (k_M + 0.0065))^{n-1}$ n : 栄養相互作用数

Arnot-Gobasモデル予測結果の信頼性 (適用範囲)

- logKow予測値 >9 の物質については、不確実性が非常に高い。
- イオンになりやすい物質、顔料と染料又はペルフルオロ化合物に本モデルを適用することは推奨しない。

(考慮事項)

- 甲殻類やプランクトンの代謝量予測モデルがなく考慮していない。これらの種で代謝されやすい物質については、過大評価となっている可能性がある。
- 本モデルでは、生物中脂質含有率「0.107 (upper), 0.0685 (middle), 0.0598 (lower)」を使用しているが、多くのラボでの実測値は0.03-0.05である。このため、回帰式による式よりも高い値を予測する可能性がある。

QSAR Toolboxを用いた BCF予測

QSAR Toolboxを用いたBCF予測の方法

QSAR Toolbox 4.6 [Document 1]

Document | Single Chemical | Chemical List | Search | IUCLID search | Target Endpoint

New | Open | Close | Save | CAS# | Name | Structure | Composition | Select | ChemIDs | Database | Inventory | List | Substructure (SMARTS) | Query | Simple | Advanced | Define

The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Documents

- Document 1
 - # [C: 1;Md: 0;P: 0] CAS: 108907
 - [C: 4;Md: 0;P: 0] test-smiles.txt

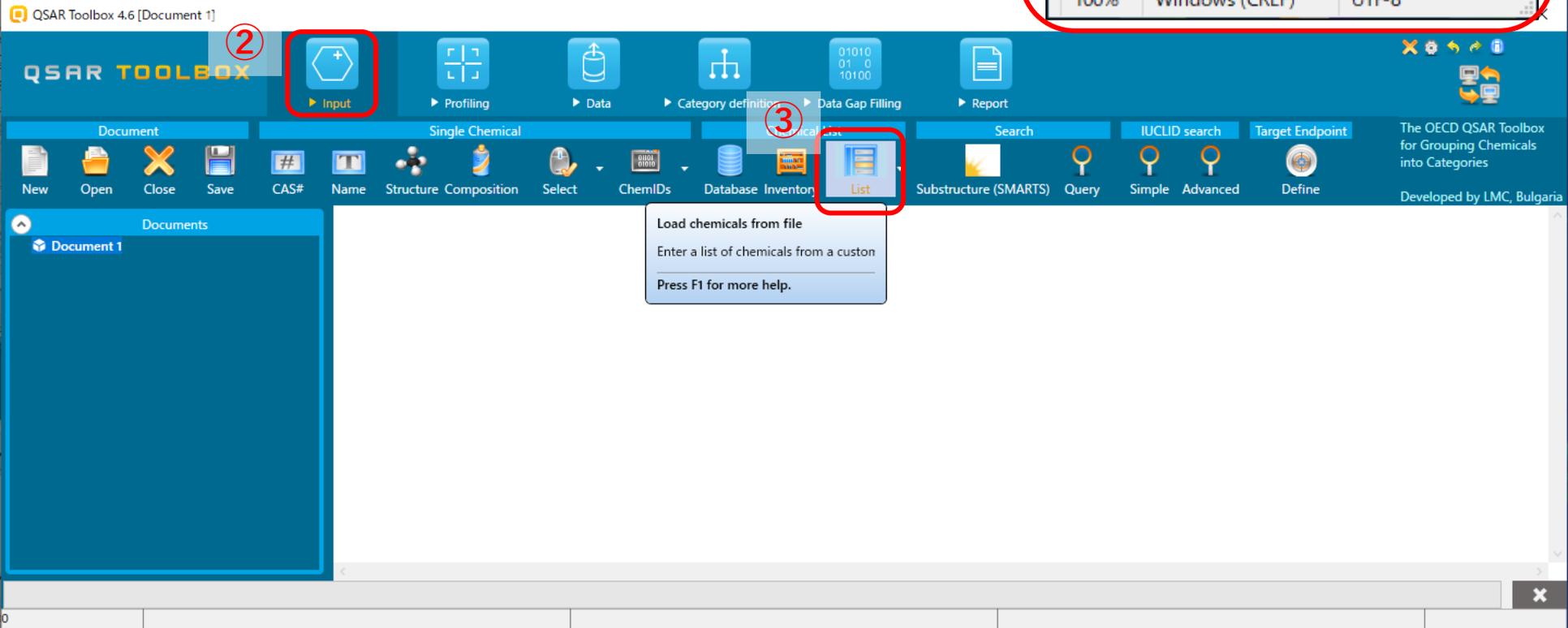
Filter endpoint tree...

	1	2	3	4
Structure				
Structure info				
Parameters				
2D				
(Q) Acidic pKa (Chemaxon)	Not calculated	Not calculated	Not calculated	Not calculated
(Q) Basic pKa (Chemaxon)	Not calculated	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS composite calculator)	Not calculated	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS Consensus)	Not calculated	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS Electric)	Not calculated	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS Regression)	Not calculated	Not calculated	Not calculated	Not calculated
Amino acids pKa (OASIS Regression)	Not calculated	Not calculated	Not calculated	Not calculated
BAF	Not calculated	Not calculated	Not calculated	Not calculated
BAF (lower trophic)	Not calculated	Not calculated	Not calculated	Not calculated
BAF (mid trophic)	Not calculated	Not calculated	Not calculated	Not calculated
BAF (upper trophic, biotransformation...)	Not calculated	Not calculated	Not calculated	Not calculated
BAF (upper trophic)	Not calculated	Not calculated	Not calculated	Not calculated
Basic pKa (OASIS Regression)	Not calculated	Not calculated	Not calculated	Not calculated
BCF	Not calculated	Not calculated	Not calculated	Not calculated
BCF (lower trophic)	1.39 log(L/kg)	2.17 log(L/kg)	2.12 log(L/kg)	2.21 log(L/kg)
BCF (mid trophic)	Not calculated	Not calculated	Not calculated	Not calculated
BCF (upper trophic, biotransformation...)	Not calculated	Not calculated	Not calculated	Not calculated
BCF (upper trophic)	Not calculated	Not calculated	Not calculated	Not calculated
Bio Half-Life	Not calculated	Not calculated	Not calculated	Not calculated

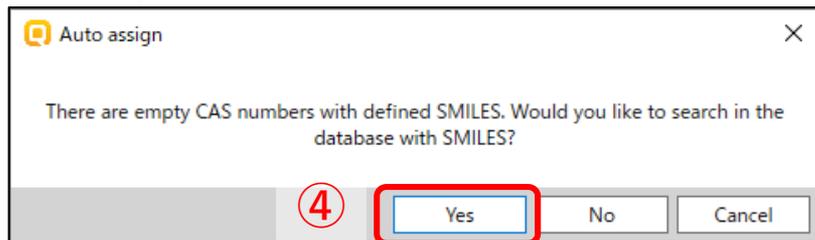
構造リストで入力する①

- ① SMILESの書かれたテキストファイルを用意する
- ② Inputタブを選択
- ③ Listを選択

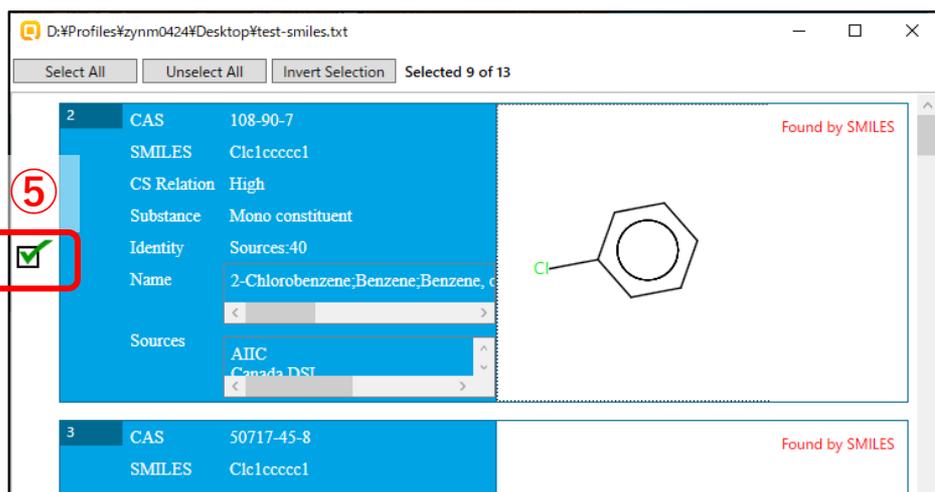
```
test-smiles.txt - メモ帳
ファイル(F) 編集(E) 書式(O) 表示(V) ヘルプ(H)
c1ccccc1Cl
c1(Cl)ccccc1Cl
c1c(Cl)cccc1Cl
c1cc(Cl)ccc1Cl
100% Windows (CRLF) UTF-8
```



構造式リストで入力する②

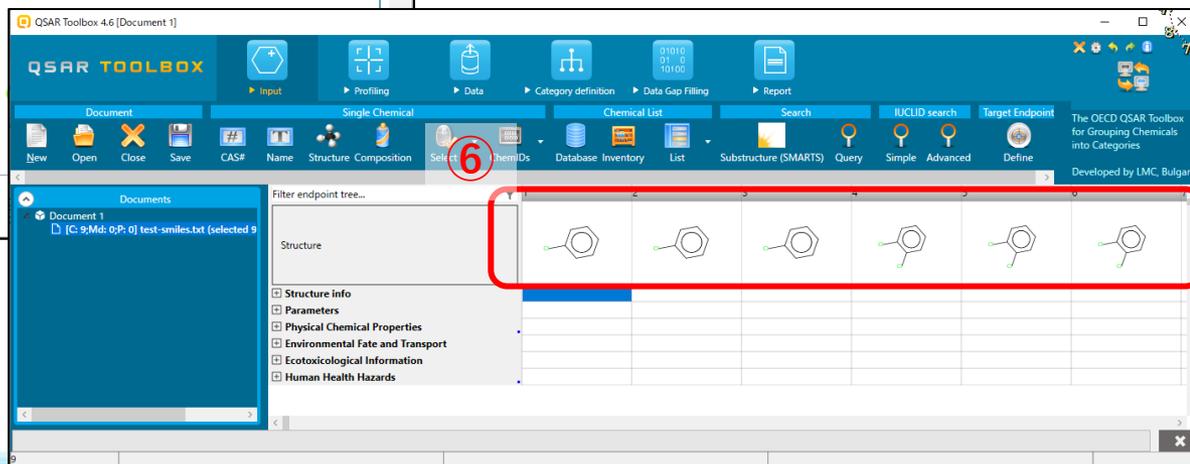


④ CAS番号を検索するか選択（データ検索をする場合はCASが必要）



⑤ CAS番号を検索した場合、QSAR Toolboxに登録されている物質のうちどのデータを使うかを選択

⑥ 構造リストが入力完了



QSAR ToolboxでのBCF計算①

The screenshot shows the QSAR Toolbox 4.6 interface. The left sidebar displays a tree view of parameters under '2D', with a red circle and the number '1' next to the 'Parameters' folder. The main window shows a table of chemical structures and their calculated parameters. The right-hand context menu is open, showing a 'Sort' option with a red circle and the number '2' next to it. The 'Sort' menu is expanded to show several options, with 'Calculate/extract selected parameters' highlighted by a red box.

Structure	1	2	3
Structure	<chem>c1ccc(Cl)cc1</chem>	<chem>c1ccc(Cl)cc1</chem>	<chem>c1ccc(Cl)cc1</chem>
Structure info			
Parameters			
2D			
(Q) Acidic pKa (Chemaxon)	Not calculated	Not calculated	Not calculated
(Q) Basic pKa (Chemaxon)	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS composite calculator)	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS Consensus)	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS Electric)	Not calculated	Not calculated	Not calculated
Acidic pKa (OASIS Regression)	Not calculated	Not calculated	Not calculated
Amino acids pKa (OASIS Regression)	Not calculated	Not calculated	Not calculated
BAF	Not calculated	Not calculated	Not calculated
BAF (lower trophic)	Not calculated	Not calculated	Not calculated
BAF (mid trophic)	Not calculated	Not calculated	Not calculated
BAF (upper trophic, biotransformation...)	Not calculated	Not calculated	Not calculated
BAF (upper trophic)	Not calculated	Not calculated	Not calculated
Basic pKa (OASIS Regression)	Not calculated	Not calculated	Not calculated
BCF	Not calculated	Not calculated	Not calculated
BCF (lower trophic)	Not calculated	Not calculated	Not calculated

① Parameters→2D (左側の+記号をクリック)

② 計算したい項目で右クリックして「Calculate / extract」のいずれかを選択

QSAR ToolboxでのBCF計算②

QSAR Toolbox 4.6 [Document 1]

Document Single Chemical Chemical List Search IUCLID search Target Endpoint

New Open Close Save CAS# Name Structure Composition Select ChemIDs Database Inventory List Substructure (SMARTS) Query Simple Advanced Define

Documents

Document 1
[C: 9;Md: 0;P: 0] test-smiles.txt (selected 9)

Filter endpoint tree...

Structure

Structure info

Parameters

2D

(Q) Acidic pKa (Chemaxon)	Not calculated	Not calculated			
(Q) Basic pKa (Chemaxon)	Not calculated	Not calculated			
Acidic pKa (OASIS composite calculator)	Not calculated	Not calculated			
Acidic pKa (OASIS Consensus)	Not calculated	Not calculated			
Acidic pKa (OASIS Electric)	Not calculated	Not calculated			
Acidic pKa (OASIS Regression)	Not calculated	Not calculated			
Amino acids pKa (OASIS Regression)	Not calculated	Not calculated			
BAF	Not calculated	Not calculated			
BAF (lower trophic)	Not calculated	Not calculated			
BAF (mid trophic)	Not calculated	Not calculated			
BAF (upper trophic, biotransformation...)	Not calculated	Not calculated			
BAF (upper trophic)	Not calculated	Not calculated			
Basic pKa (OASIS Regression)	Not calculated	Not calculated			
BCF	1.54 log(L/kg)	.54 log(L/kg)	1.54 log(L/kg)	1.93 log(L/kg)	1.93 log(L/kg)
BCF (lower trophic)	Not calculated				

EPIWIN Report

Log BCF (regression-based estimate): 1.54 (BCF = 34.7 L/kg wet-wt)
Biotransformation Half-Life (days): 0.532 (normalized to 10 g fish)
Log BAF (Arnot-Gobas upper trophic): 1.40 (BAF = 25 L/kg wet-wt)

Experimental BCF-kM Database Structure Match:

Name : Benzene, chloro-
CAS Num : 000108-90-7
Log BCF : 1.25 (BCF = 17.8 L/kg wet-wt)
BCF Data : BCF NonIonic Training Set
Log Bio HL: -1.019 (Bio Half-life = 0.0957 days)
Bio Data : kM Training Set

Log Kow (experimental): 2.84
Log Kow used by BCF estimates: 2.84

Equation Used to Make BCF estimate:
Log BCF = 0.6598 log Kow - 0.333 + Correction

Correction(s): Value
No Applicable Correction Factors

Estimated Log BCF = 1.541 (BCF = 34.74 L/kg wet-wt)

Whole Body Primary Biotransformation Rate Estimate for Fish:

TYPE	NUM	LOG BIOTRANSFORMATION FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic chloride [-CL]	0.3778	0.3778
Frag	1	Hydrocarbon aromatic group [-C6H5]	0.6002	0.6002

Close

③ BCF予測値をダブルクリック

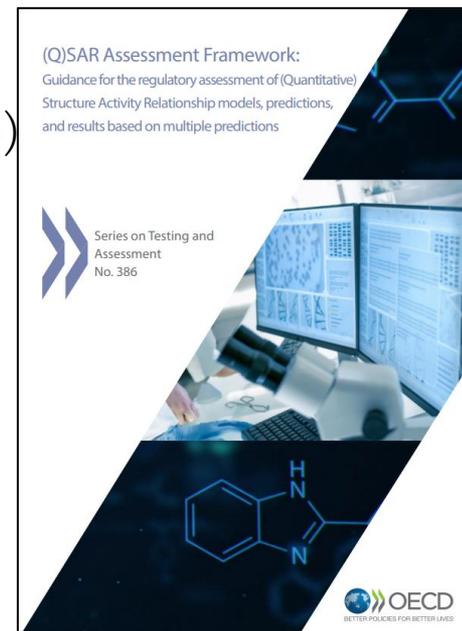
④ 計算結果の詳細が確認可能

最新動向： QSAR Assessment Framework

QSAR Assessment Framework

QSAR予測結果を規制のために使用できるか
チェックリストをもとに評価する枠組み

- 基本事項をまとめたガイダンスを策定
Guidance for the regulatory assessment of (Quantitative) Structure Activity Relationship models, predictions, and results based on multiple predictions
- チェックリストを使用して評価
 - QSARモデルチェックリスト
 - 予測チェックリスト
 - 結果チェックリスト(複数モデルの予測を組み合わせて評価する場合)
- NIHS、JaCVAM、NITEもワーキンググループに参画



ご静聴ありがとうございました

- 分解性QSAR：BIOWIN5、6
- 蓄積性QSAR：BCFBAF
- QSAR Toolboxを用いたBCF予測
- 最新動向：QSAR Assessment Framework

ご質問等はこちらへ hess@nite.go.jp