Endpoint “Bioconcentration Factor” (BCF)

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Definition – substances

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

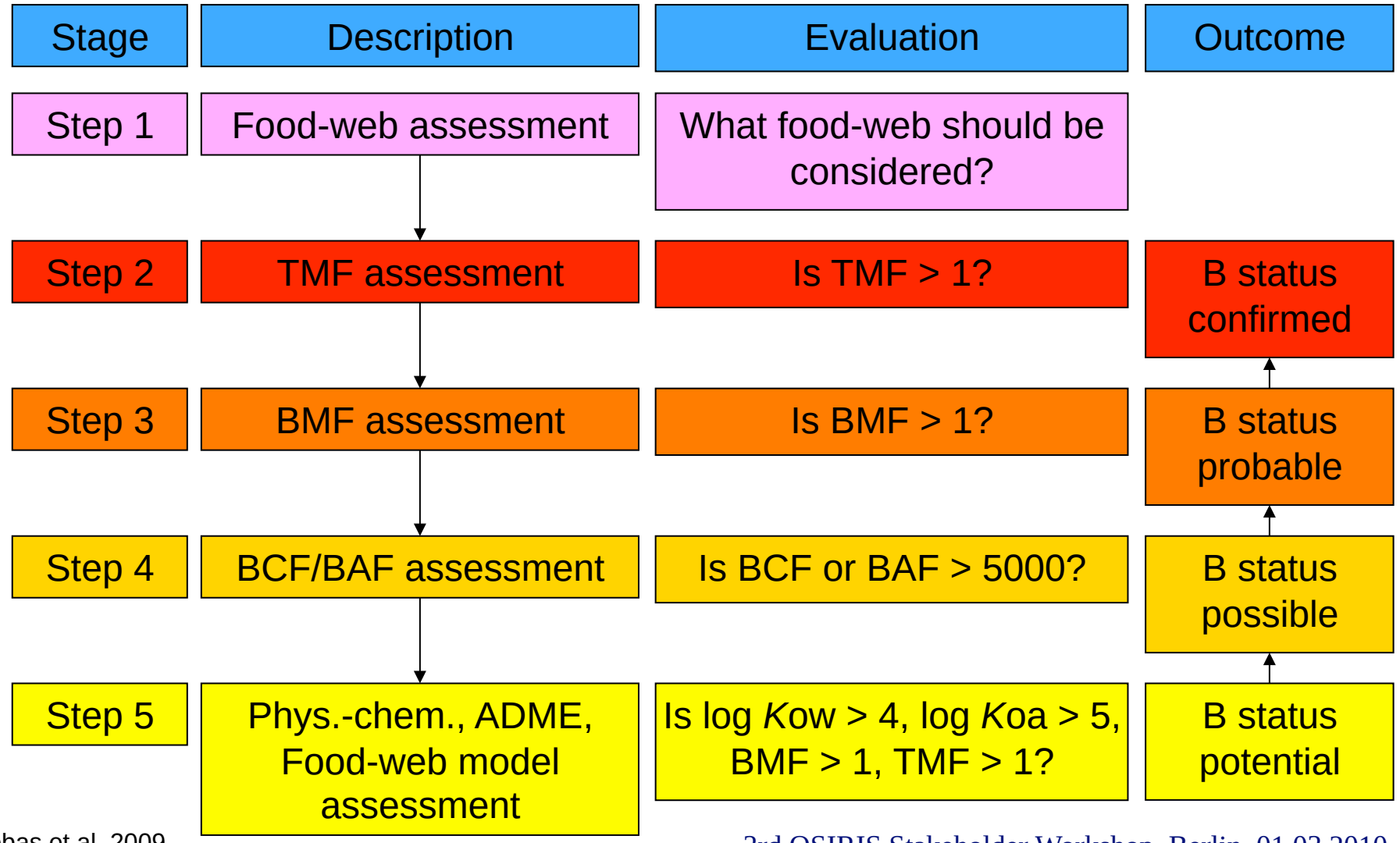
Gobas et al. 2009. Revisiting bioaccumulation criteria for POPs and PBT assessments. IEAM 5 (4), 624–637.

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



Gobas et al. 2009.
Revisiting bioaccumulation criteria for POPs and PBT assessments. IEAM 5 (4), 624–637.

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REACH ANNEX XIII

A substance fulfils the **bioaccumulation criterion (B-)** when:

– the bioconcentration factor (BCF) is higher than **2 000**.

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 **5 000**.

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Comparison of quantitative B-criteria (BCF (BioConcentration Factor), BAF (BioAccumulation Factor), log K_{OW} (1-octanol/water partition coefficient)).

Institution/Authors	BCF	log *K*ow
Kelly et al. 2007	---	> 2
Brown & Wania 2008	---	> 3,5
CLP Regulation	> 100 **> 500**	>3 **>4**
OSPAR	> 500	>4
CPA Green Screen	> 1000	> 4,5
Washington State	> 1000	> 5
US EPA	> 1000	---
REACH ESIS KEMI Schweden DK EPA	**> 2000**	> 3, > 4,5
Stockholm Convention EU POP Environment Canada	> 5000	> 5

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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)

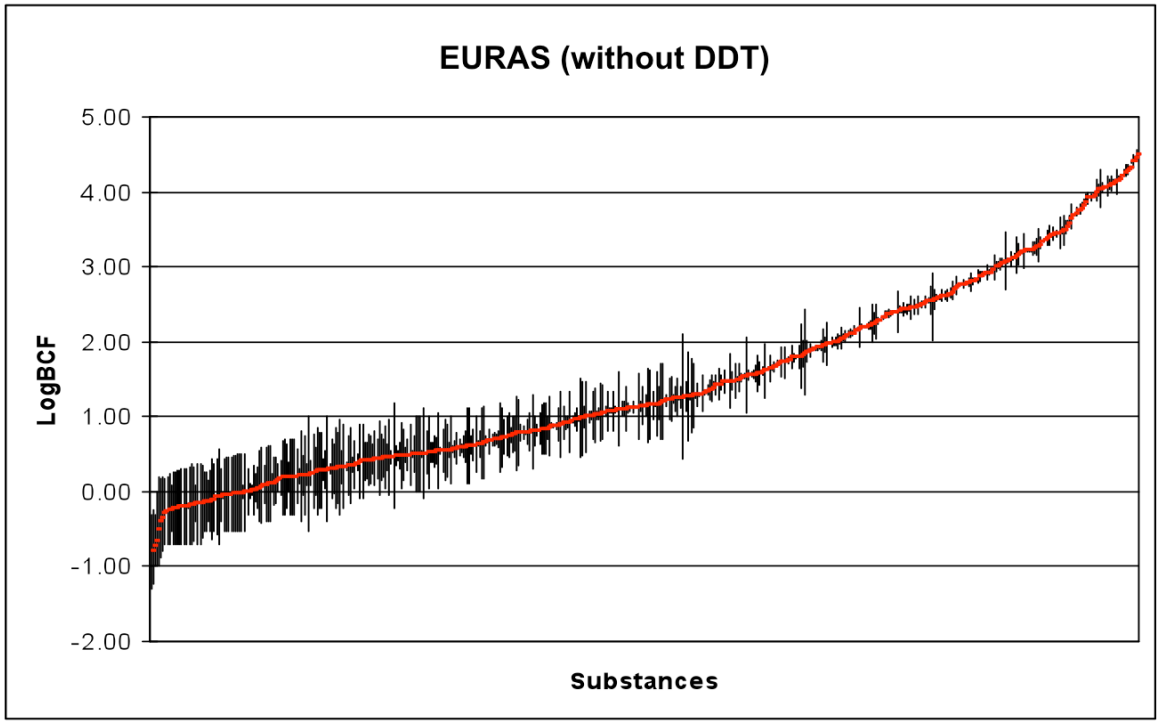
- ✓ 842 compounds
- ✓ Single or multiple BCF values
- ✓ Reliability score

EURAS DS

Experimental variability

	n substances	max SD	average SD	max range	SD%> 0.3
EURAS (without DDT*)	542	1.40	0.30	3.57	37.08

* Very high variability (3.57 log units)



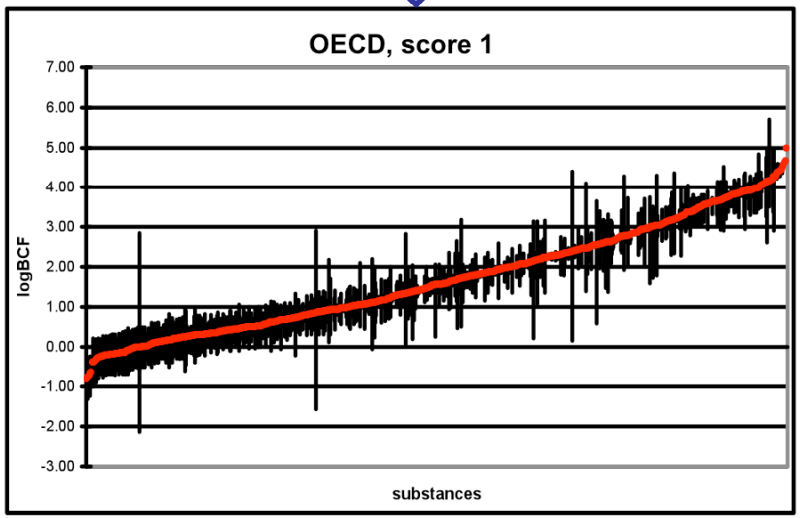
465 compounds with multiple values

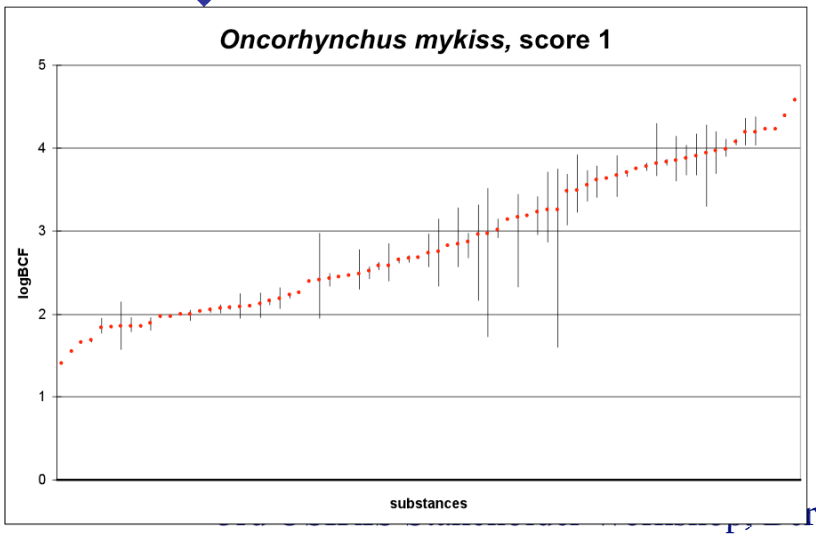
Range < 0.4 log units for 60% of compounds

Arnot DS

Experimental variability

Fish	Overall score	n substances	max SD	average SD	max range	% SD> 0.3
all	*all*	759	1.20	0.34	4.99	41.24
all	*1*	621	1.24	0.29	2.99	34.30
OECD	*all*	700	1.30	0.32	4.99	39.57
OECD	*1*	595	0.96	0.28	2.69	32.27
Oncorhynchus mykiss	*all*	117	0.82	0.26	2.72	27.35
Oncorhynchus mykiss	*1*	75	0.58	0.12	2.16	8.00





403 compounds

with multiple values

Range < 0.4

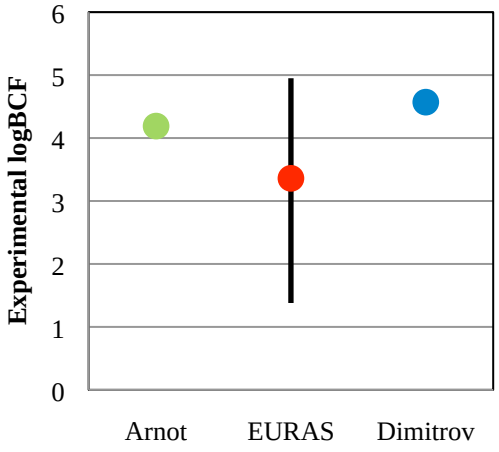
log units

(58% comp.)

Inter/intra databases experimental variability

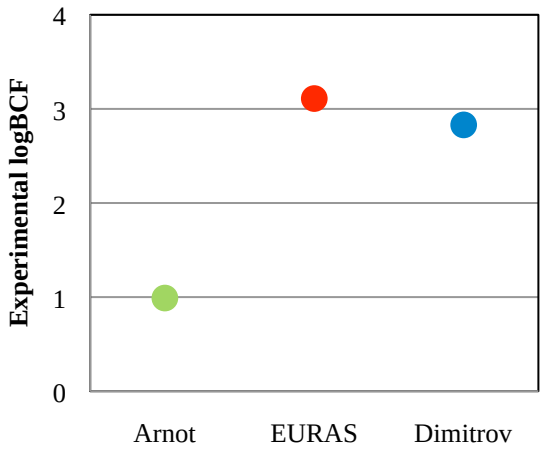
300 common compounds ⟹ Range < 0.4 log units = 45%

DDT



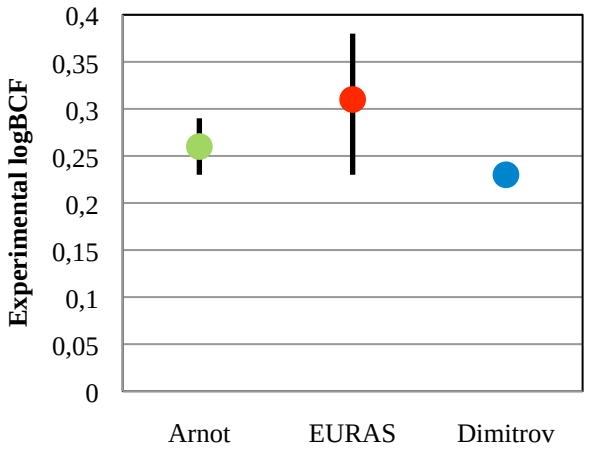
Intra DB high variability

9,10-Anthracene dione, 2-ethyl-



Inter DB high variability

2-Propanol, 1,1,1-trichloro-2-methyl-



Concordance

2. Question to stakeholders:

How much uncertainty is acceptable?

Example later: how to combine evidences

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(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.: LogBCF = 0.76·logP - 0.31

Estimation software

- EPISuite

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

	LogP	Equation
Ionic compounds	<5	LogBCF = 0.50
	5 - 6	LogBCF = 0.75
	6 - 7	LogBCF = 1.75
	7 - 9	LogBCF = 1.00
	> 9	LogBCF = 0.50
Non-ionic compounds	< 1	logBCF = 0.50
	1 - 7	logBCF = 0.6598*logP - 0.333 + ∑ correction factors
	> 7	logBCF = - 0.79*logP + 7.554 + ∑ correction factors

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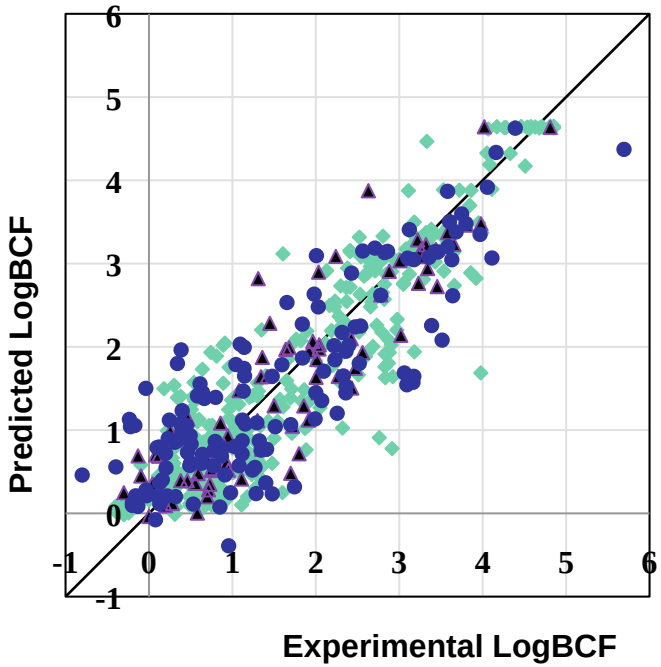
Estimation software

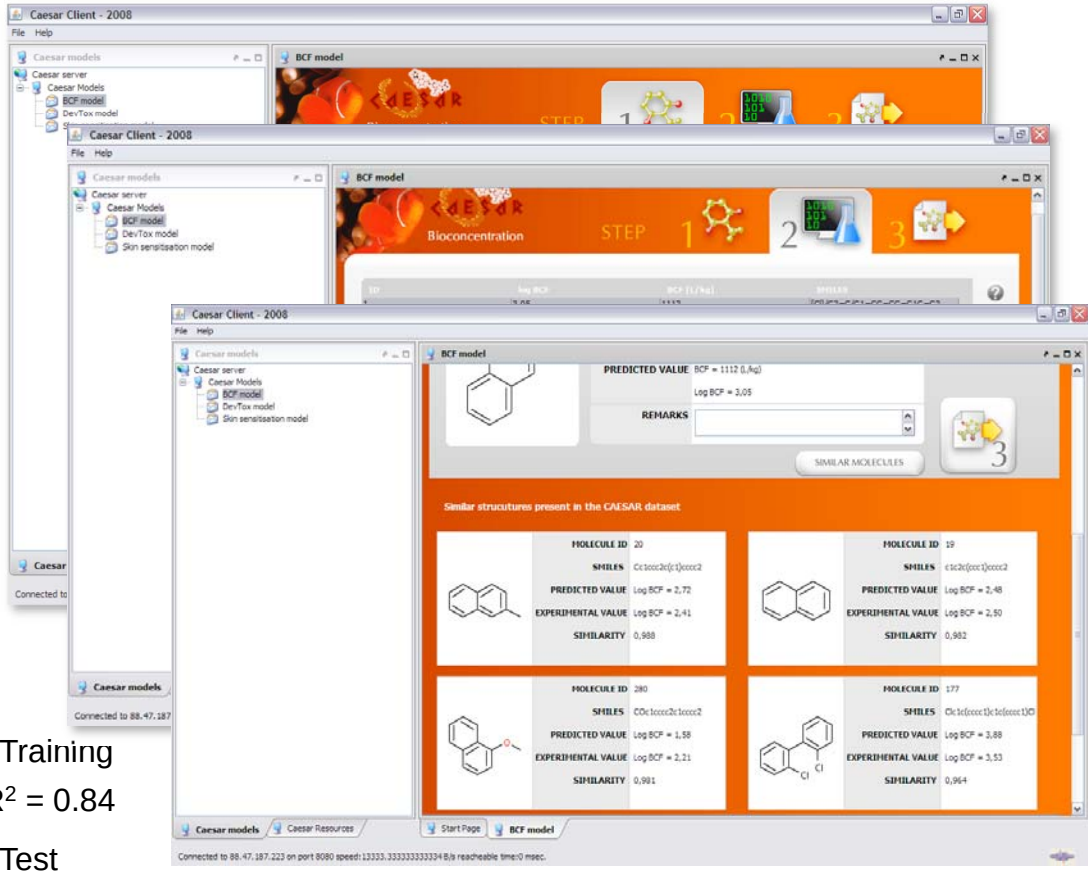
- CAESAR



Training
R^2 = 0.84

Test
R^2 = 0.81

External
R^2 = 0.71



www.caesar-project.eu

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

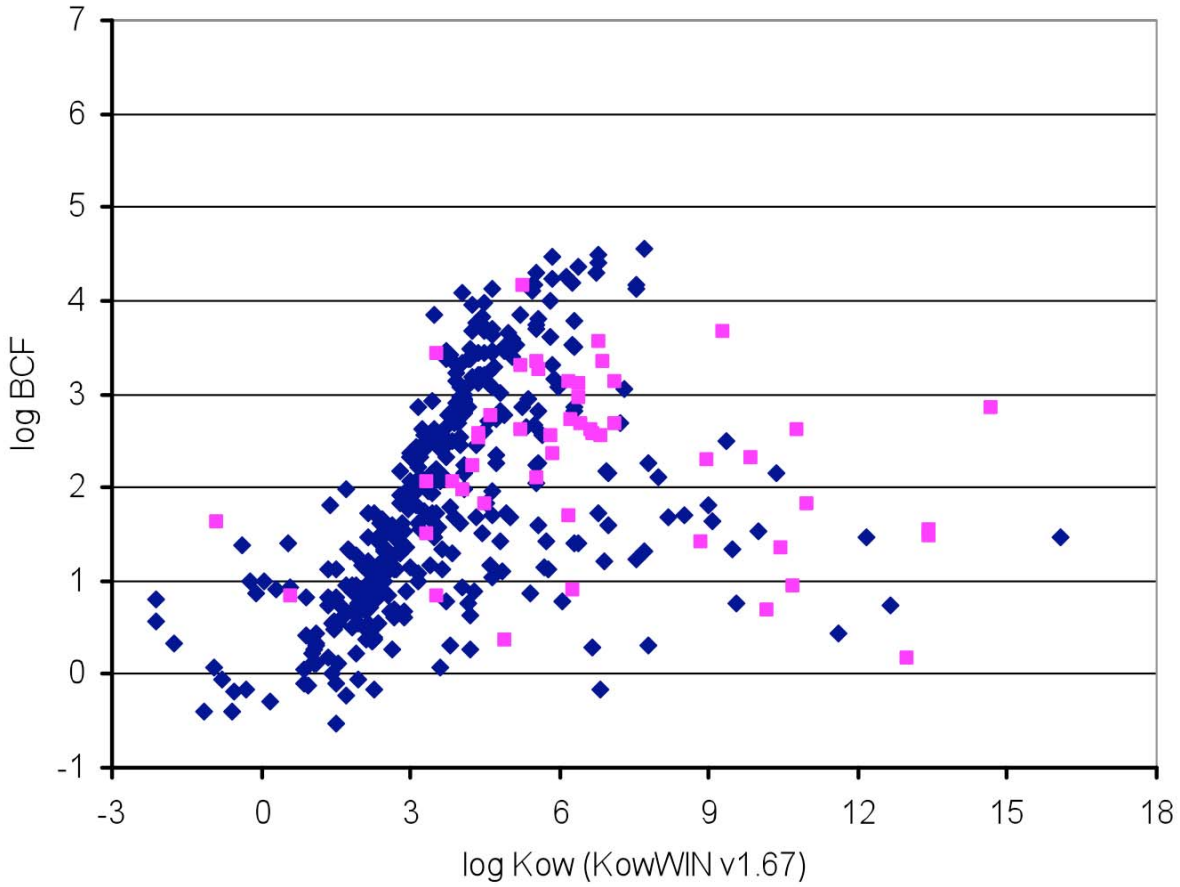
42 nonB, 7 B or vB (14 %); log BCF: 0.18 to 4.17; log K_{OW}: -0.89 to > 10; MW: 298 to 1061 g/mol

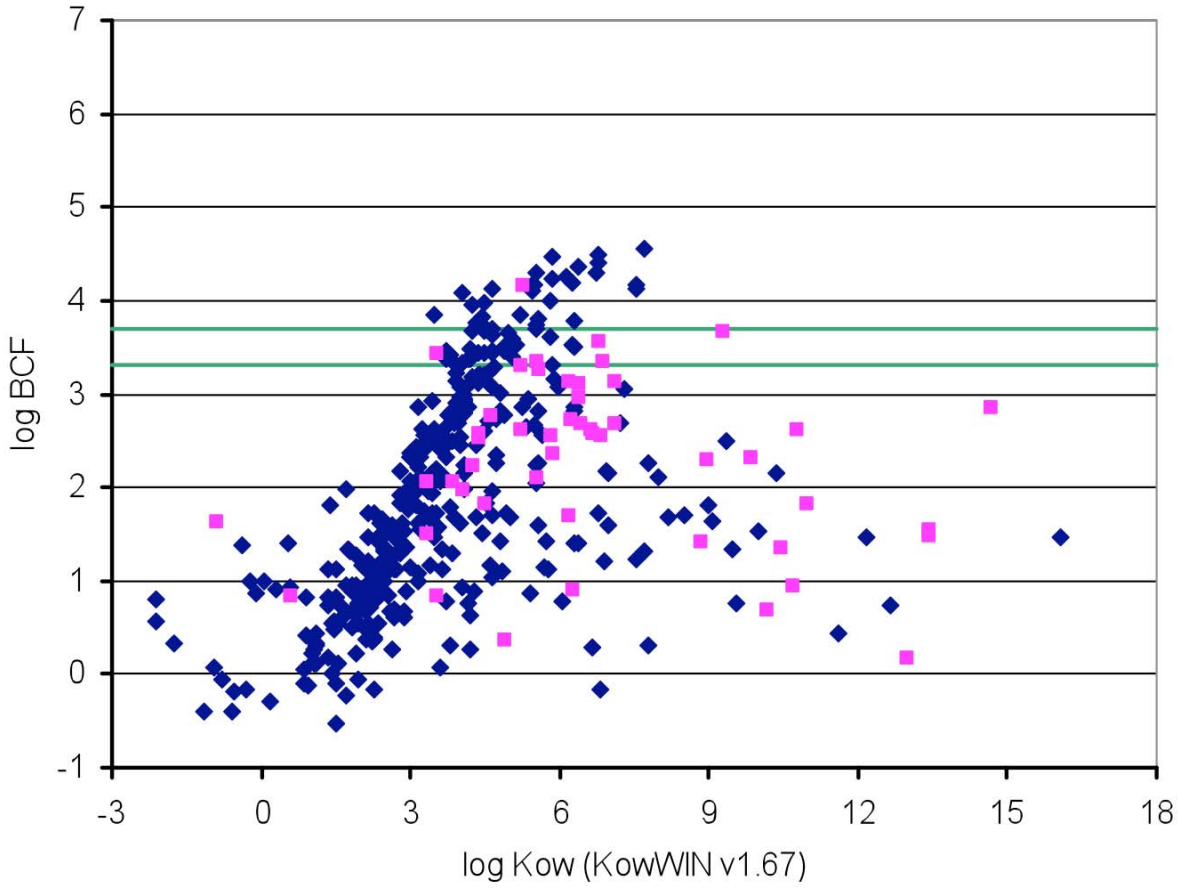
- **confirmation dataset:** 83 known B/vB chemicals

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
- SPARC on-line calculator
  based on linear solvation energy relationships
  http://ibmlc2.chem.uga.edu/sparc/


log BCF
7
6
5
4
3
2
1
0
-1
-3
0
3
6
9
12
15
18
log Kow (KowWIN v1.67)


log BCF
7
6
5
4
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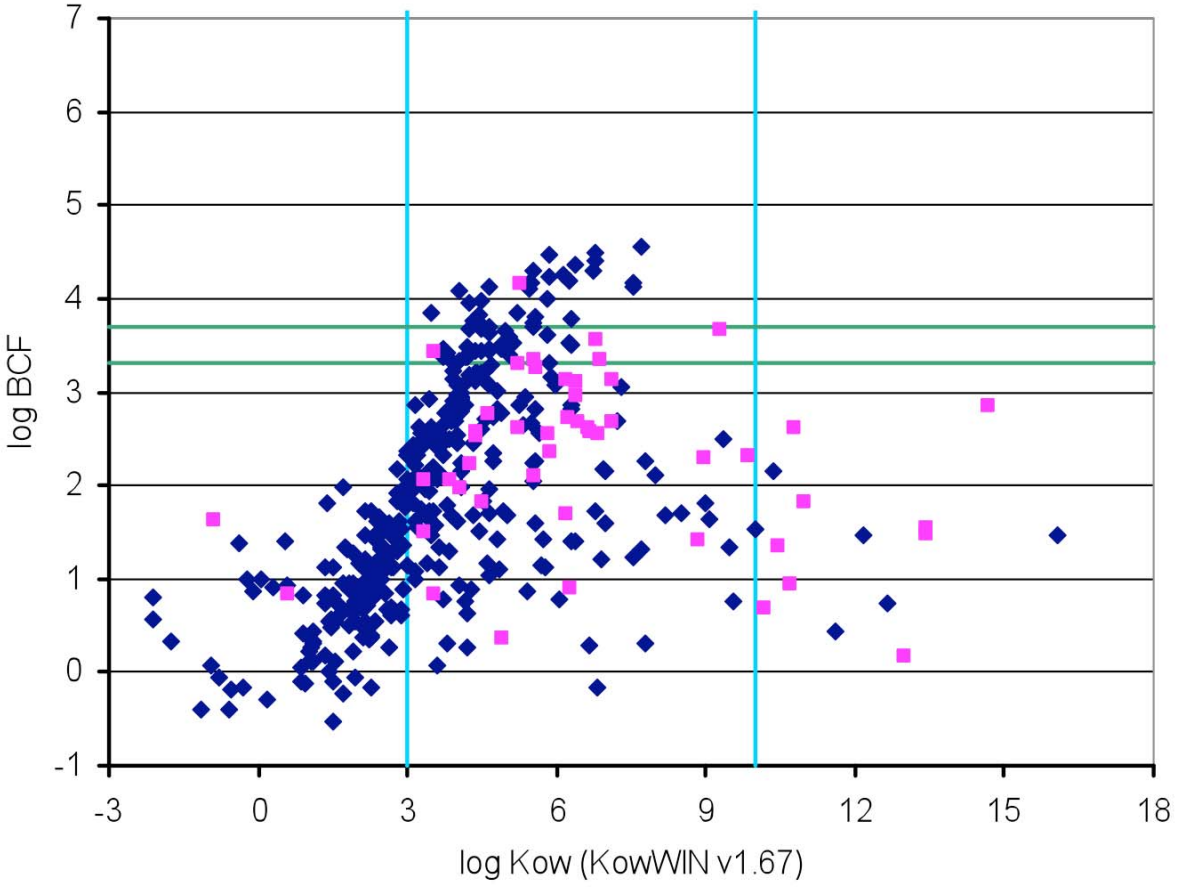
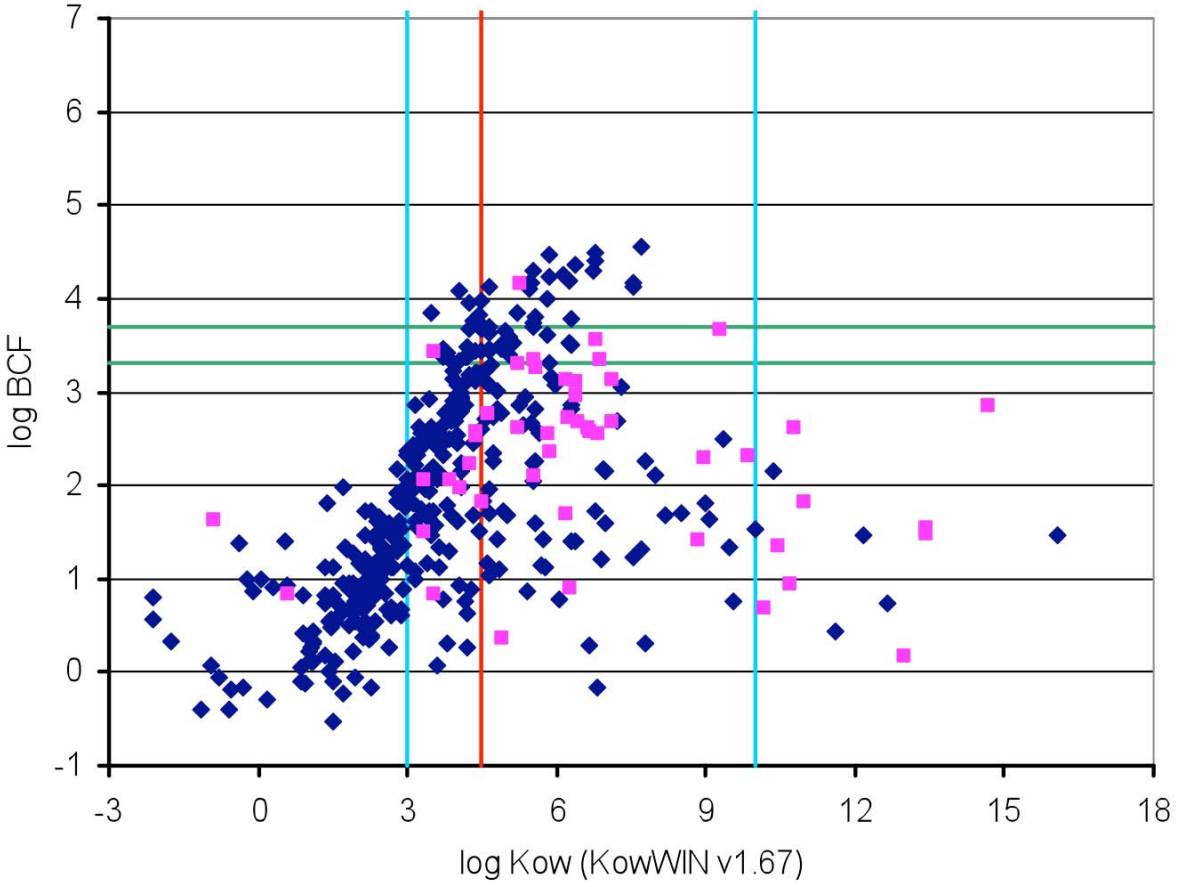
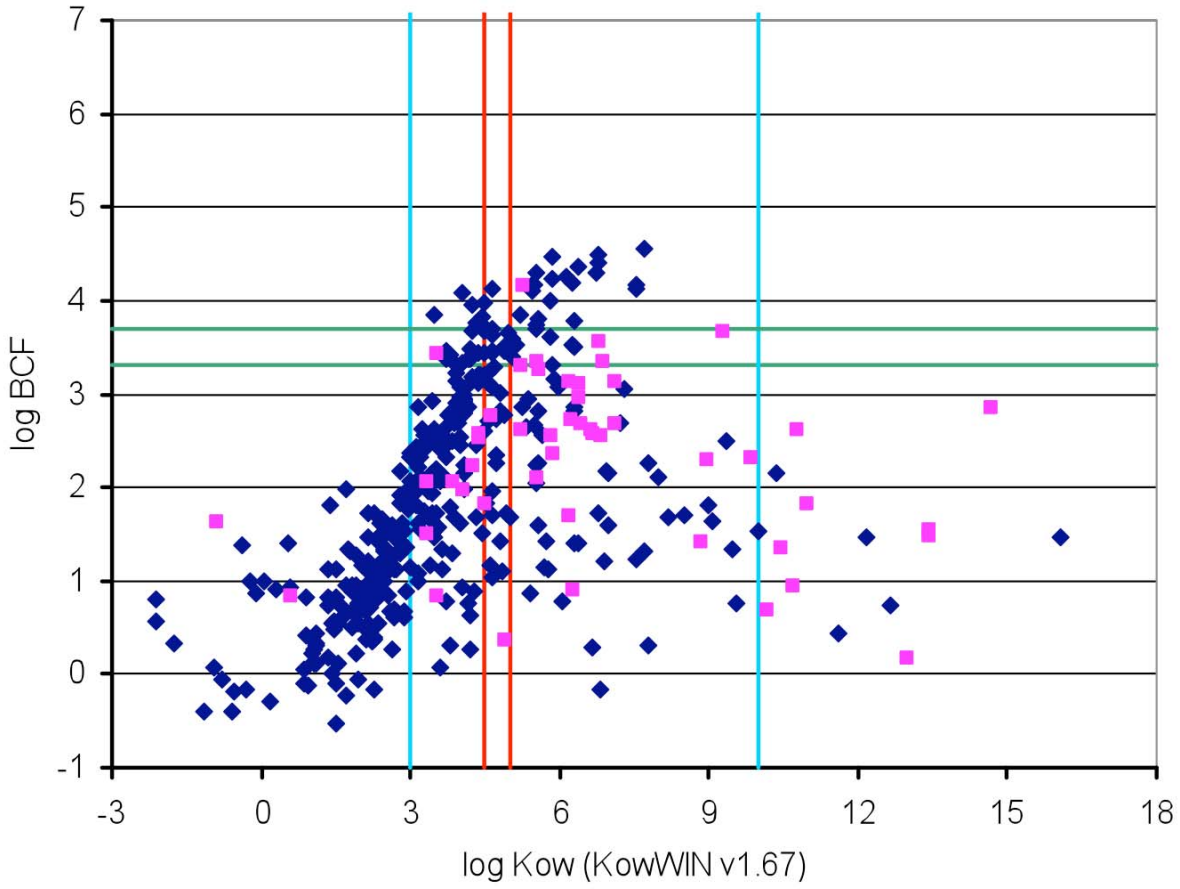
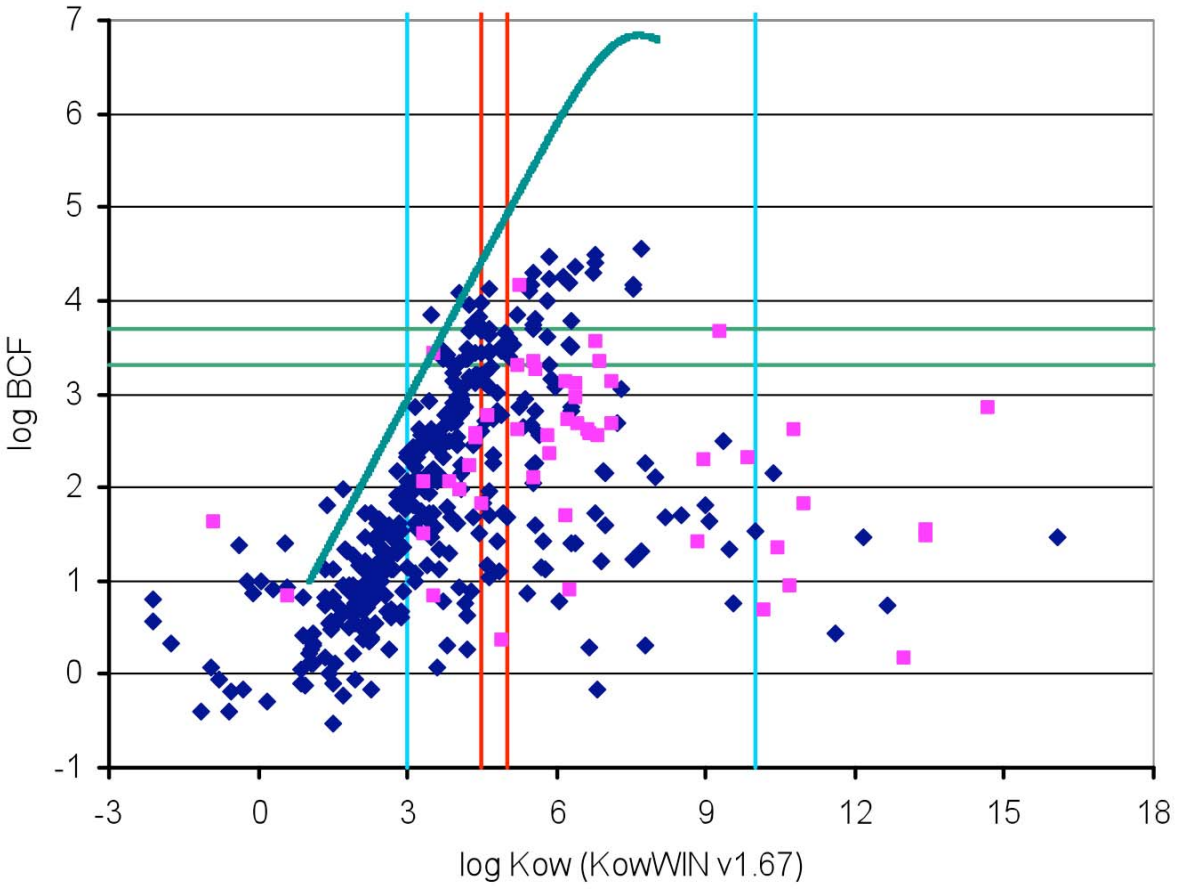
2
1
0
-1
-3
0
3
6
9
12
15
18
log Kow (KowWIN v1.67)

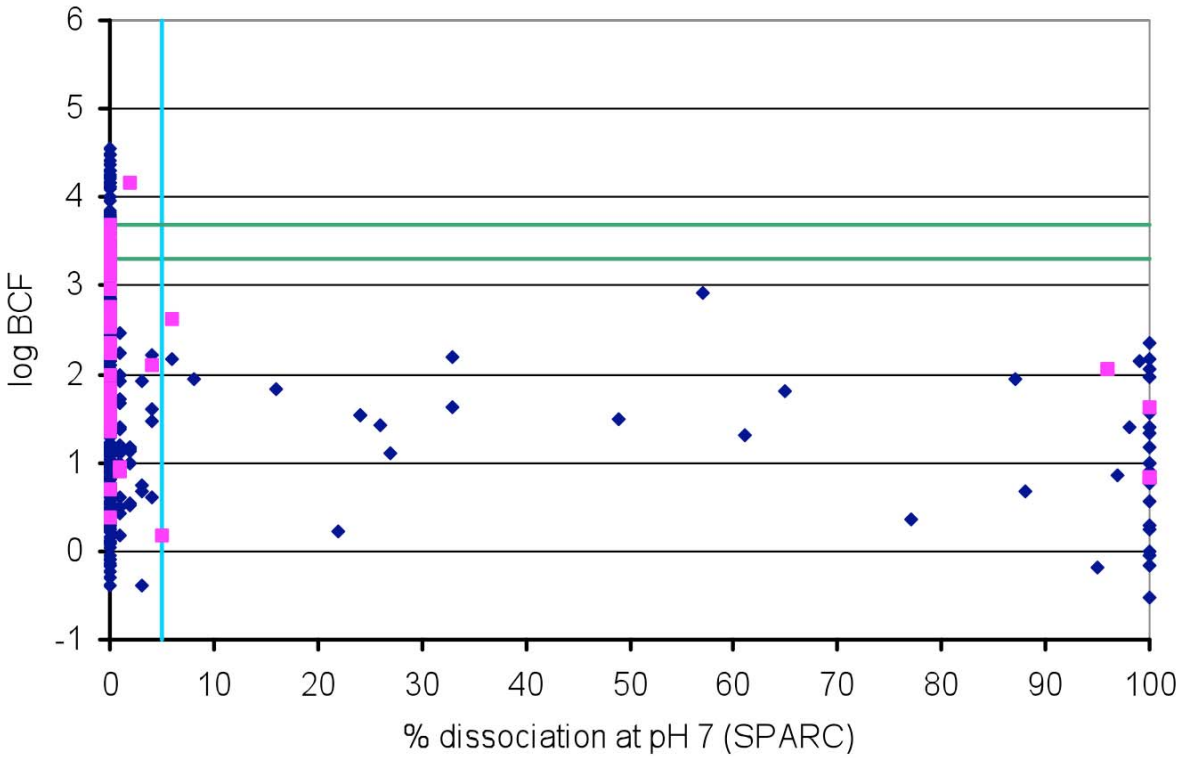

log BCF
7
6
5
4
3
2
1
0
-1
-3
0
3
6
9
12
15
18
log Kow (KowWIN v1.67)

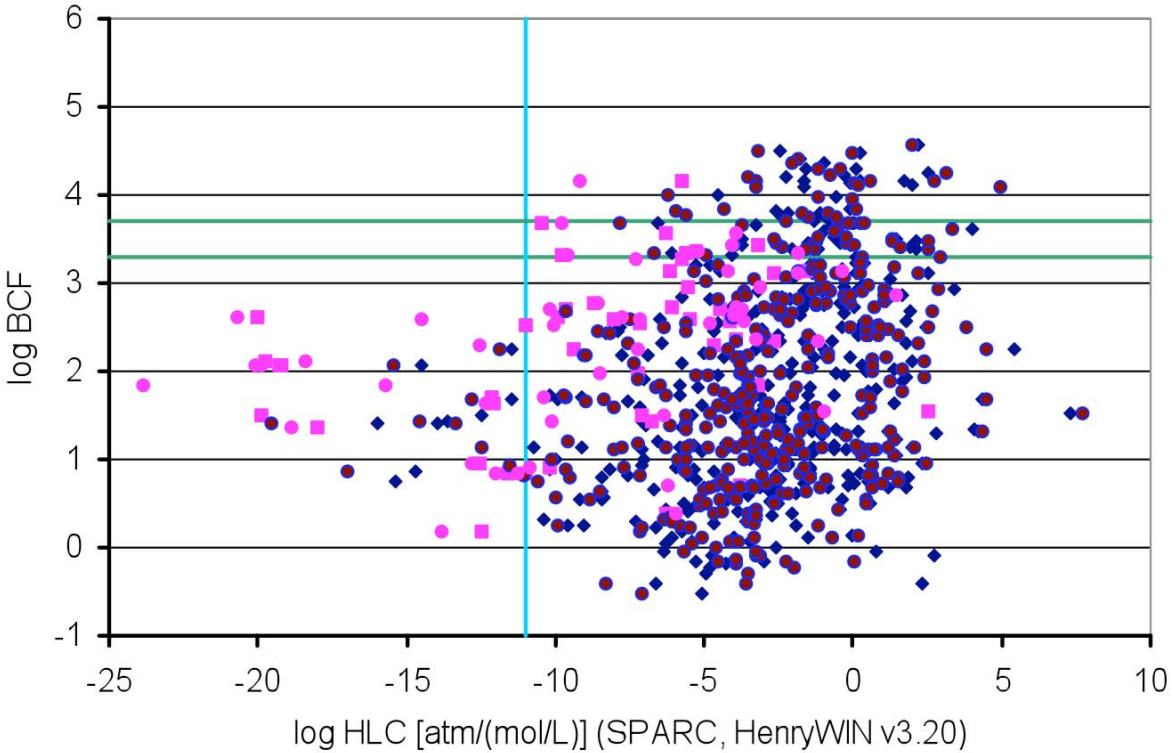

7
6
5
4
3
2
1
0
-1
log BCF
-3
0
3
6
9
12
15
18
log Kow (KowWIN v1.67)

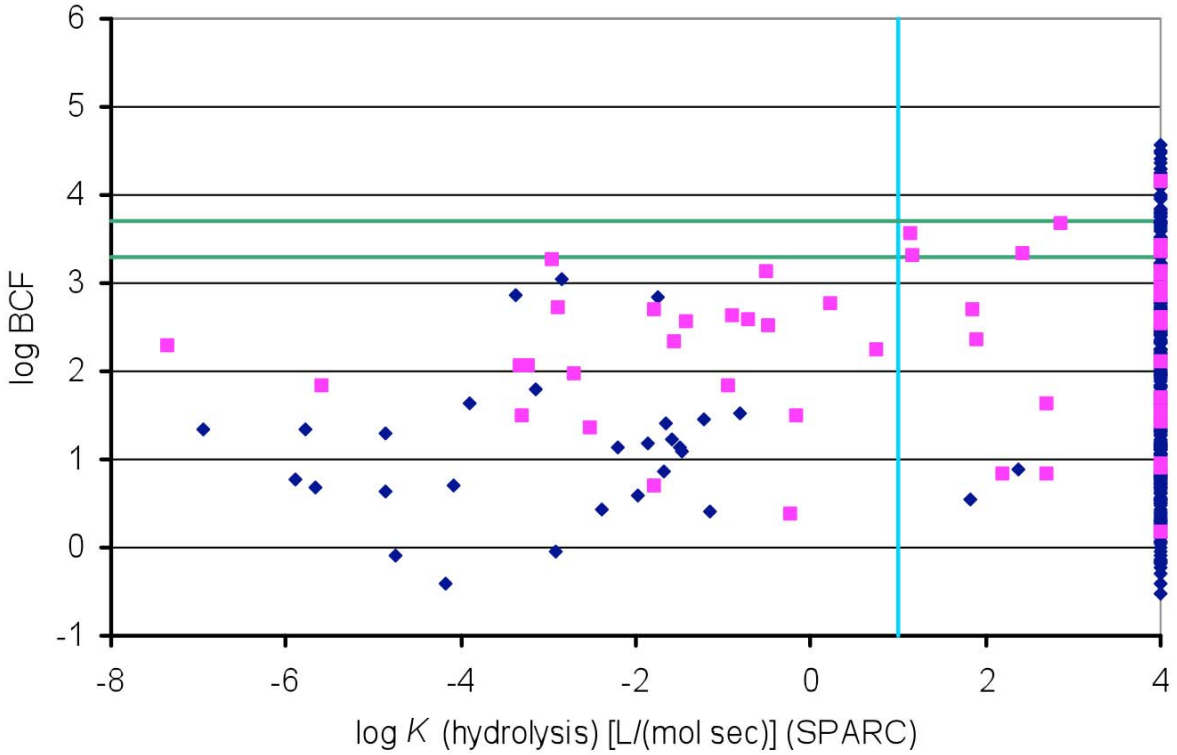

log BCF
7
6
5
4
3
2
1
0
-1
-3
0
3
6
9
12
15
18
log Kow (KowWIN v1.67)

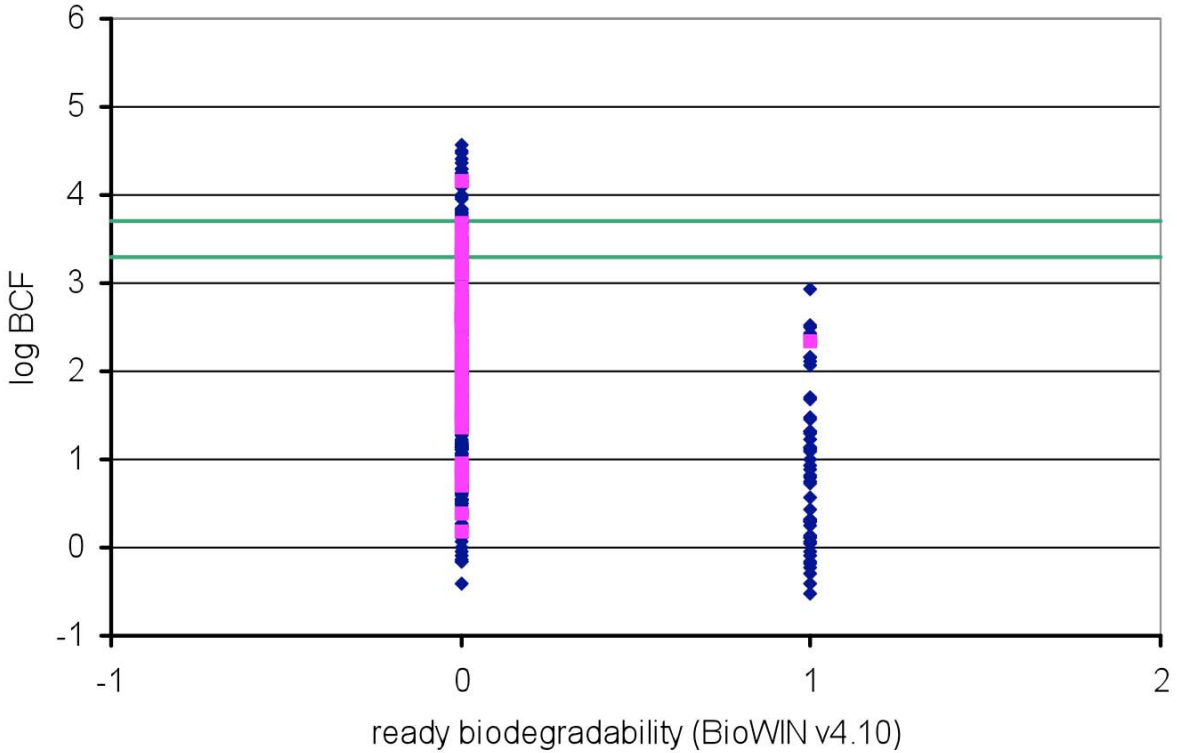

log BCF
7
6
5
4
3
2
1
0
-1
-3
0
3
6
9
12
15
18
log Kow (KowWIN v1.67)

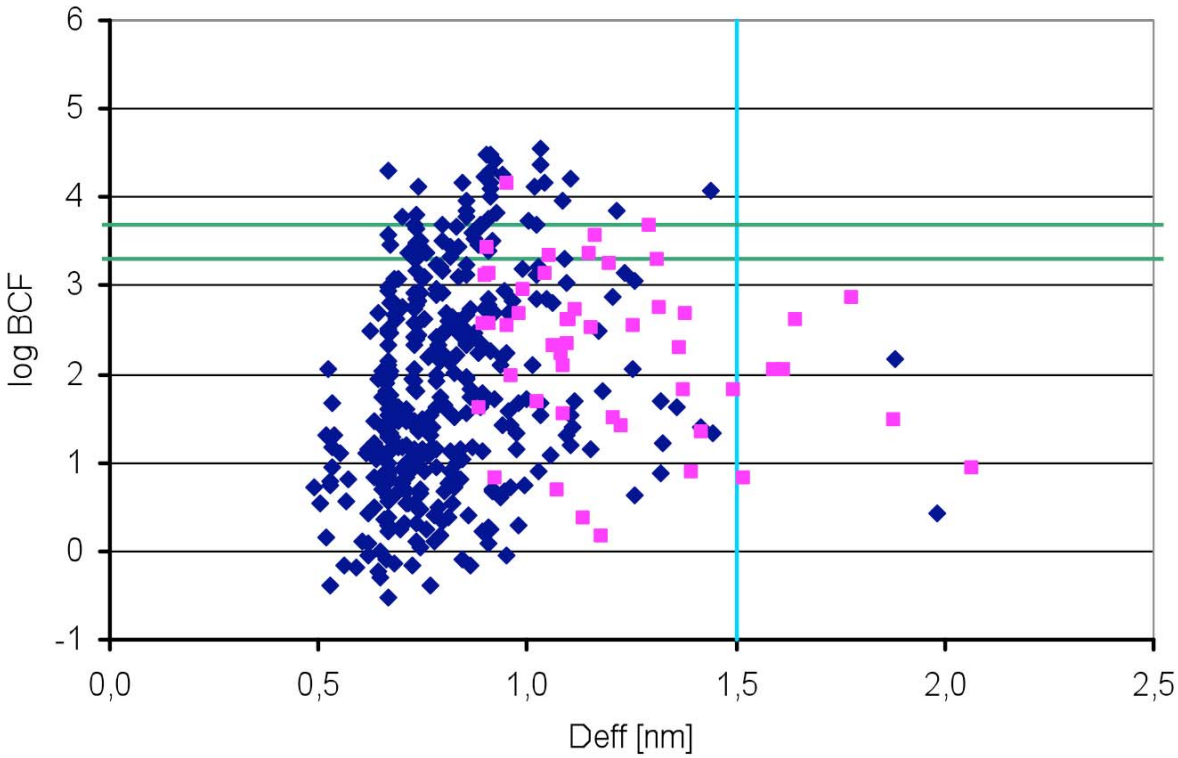
	log *K*ow < 3	log *K*ow 3 - 4.5	log *K*ow 4.5 - 10	log *K*ow > 10
T-Set: nonB	148	109	63	5
B	0	18	39	0
V-Set: nonB	2	9	22	9
B	0	1	6	0
C-Set: nonB	0	0	0	0
B	2	3	77	1

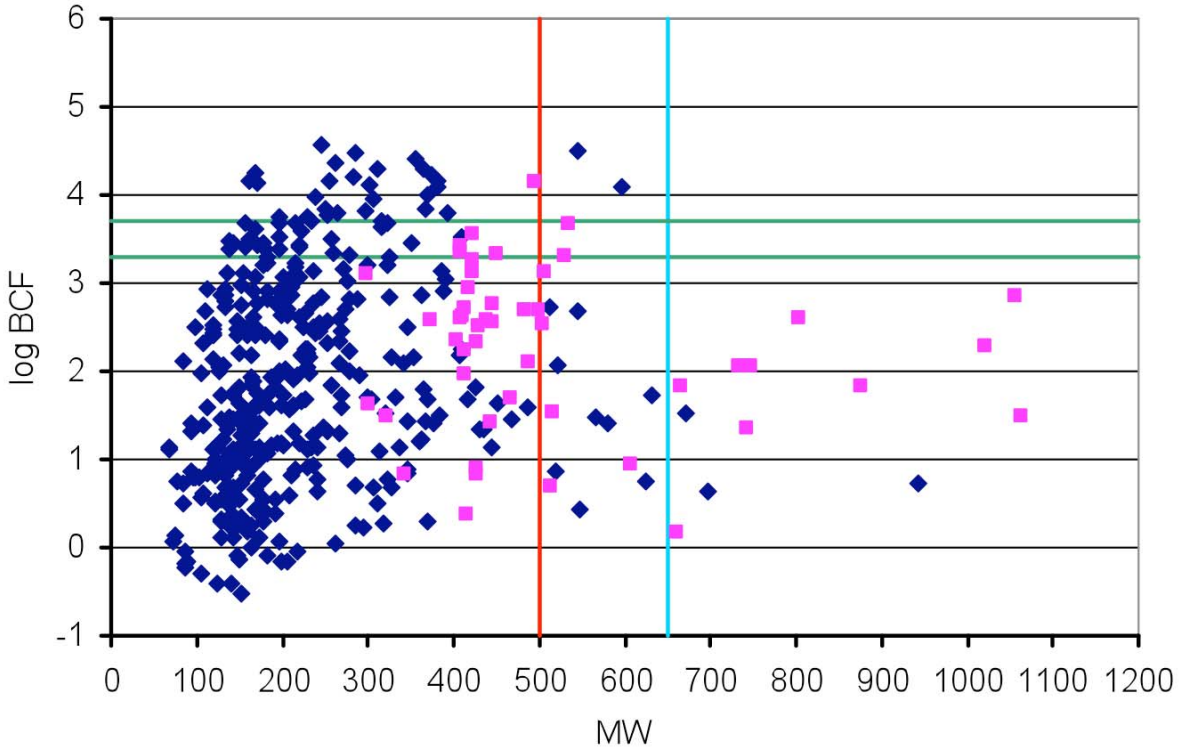

log BCF
6
5
4
3
2
1
0
-1
0
10
20
30
40
50
60
70
80
90
100
% dissociation at pH 7 (SPARC)


6
5
4
3
2
1
0
-1
log BCF
-25
-20
-15
-10
-5
0
5
10
log HLC [atm/(mol/L)] (SPARC, HenryWIN v3.20)


6
5
4
3
2
1
0
-1
log BCF
-8
-6
-4
-2
0
2
4
log K (hydrolysis) [L/(mol sec)] (SPARC)


6
5
4
3
2
1
0
-1
log BCF
-1
0
1
2
ready biodegradability (BioWIN v4.10)


6
5
4
3
2
1
0
-1
log BCF
0,0
0,5
1,0
1,5
2,0
2,5
Deff [nm]


log BCF
6
5
4
3
2
1
0
-1
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
MW

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): $\frac{TN}{Tot} \times 100$

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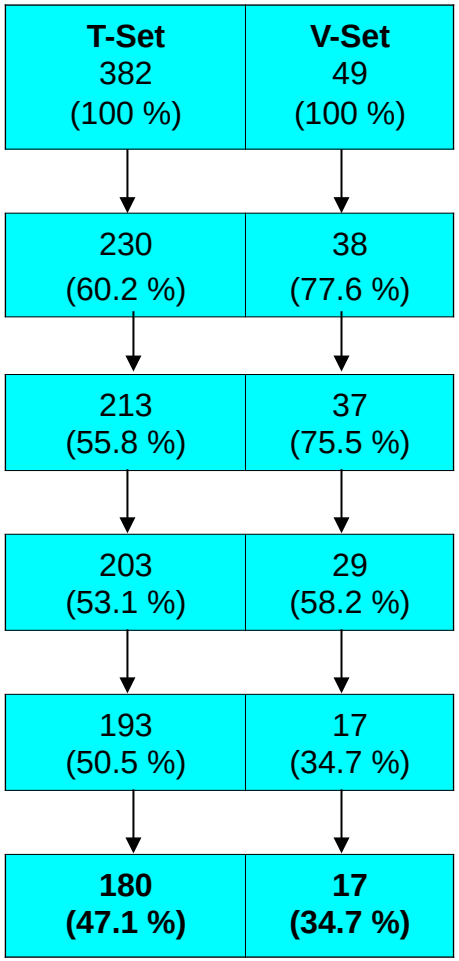
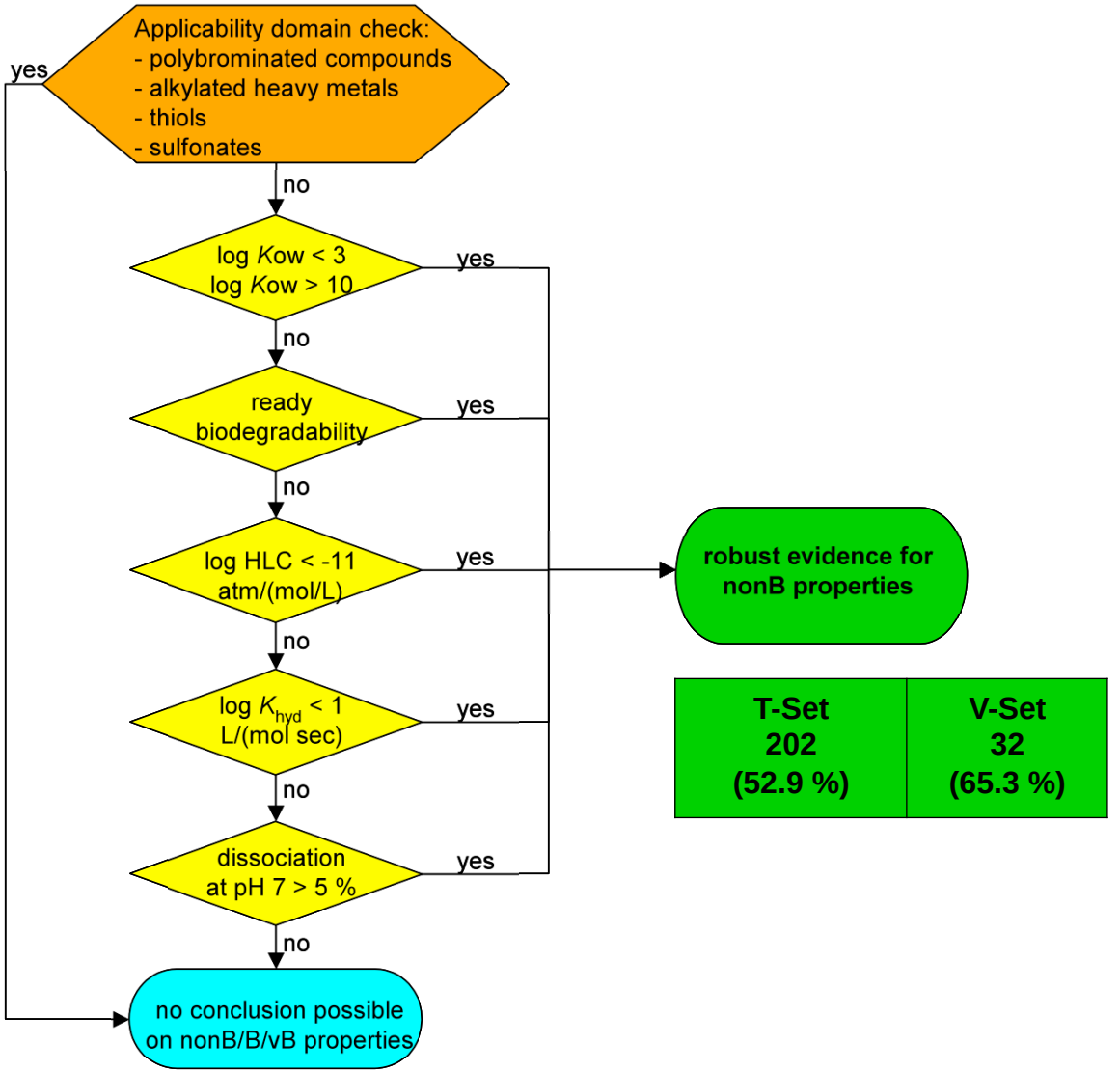
Classification statistics:

	Accuracy	Sensitivity	Specificity	Efficacy
log K_{OW} T-Set	55.0 %	100 %	47.1 %	40.1 %
log K_{OW} V-Set	36.7 %	100 %	26.2 %	22.4 %
Dissociation T-Set	25.7 %	100 %	13.8 %	11.5 %
Dissociation V-Set	28.6 %	100 %	17.1 %	14.3 %
Henry Constant T-Set	18.3 %	100 %	4.0 %	3.4 %
Henry Constant V-Set	49.0 %	100 %	40.5 %	34.7 %
Hydrolysis T-Set	22.0 %	100 %	8.3 %	7.1 %
Hydrolysis V-Set	59.2 %	100 %	52.4 %	44.9 %
Biodegradability T-Set	27.7 %	100 %	15.1 %	12.8 %
Biodegradability V-Set	16.3 %	100 %	2.4 %	2.0 %
Combined model T-Set	67.8 %	100 %	62.2 %	52.9 %
Combined model V-Set	79.6 %	100 %	76.2 %	65.3 %

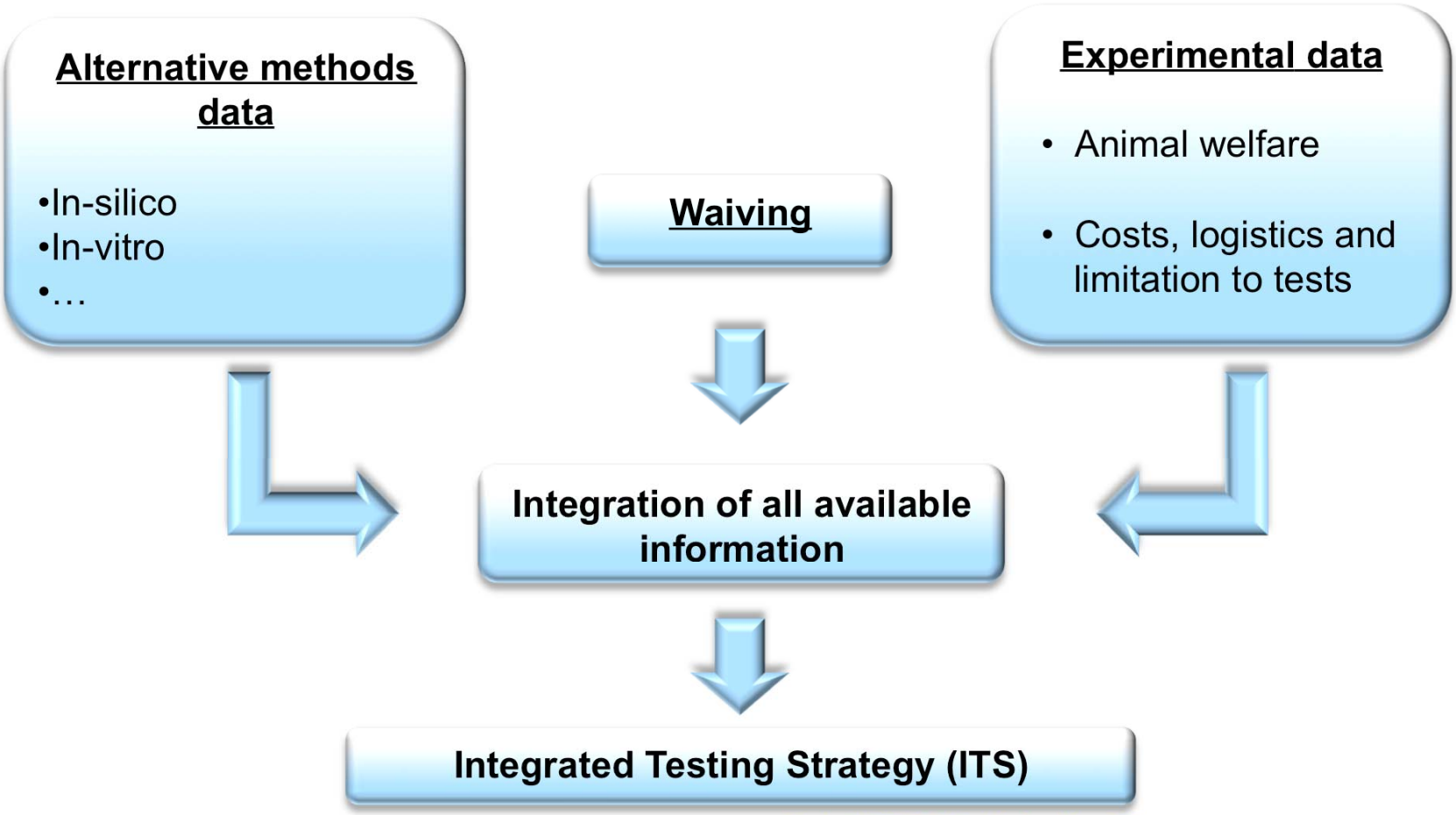

T-Set
382
(100 %)
V-Set
49
(100 %)
230
(60.2 %)
38
(77.6 %)
213
(55.8 %)
37
(75.5 %)
203
(53.1 %)
29
(58.2 %)
193
(50.5 %)
17
(34.7 %)
180
(47.1 %)
17
(34.7 %)


Applicability domain check:
- polybrominated compounds
- alkylated heavy metals
- thiols
- sulfonates
yes
no
log Kow < 3
log Kow > 10
yes
no
ready
biodegradability
yes
no
log HLC < -11
atm/(mol/L)
yes
no
log K_hyd < 1
L/(mol sec)
yes
no
dissociation
at pH 7 > 5 %
yes
no
no conclusion possible
on nonB/B/vB properties
robust evidence for
nonB properties
T-Set
202
(52.9 %)
V-Set
32
(65.3 %)

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?



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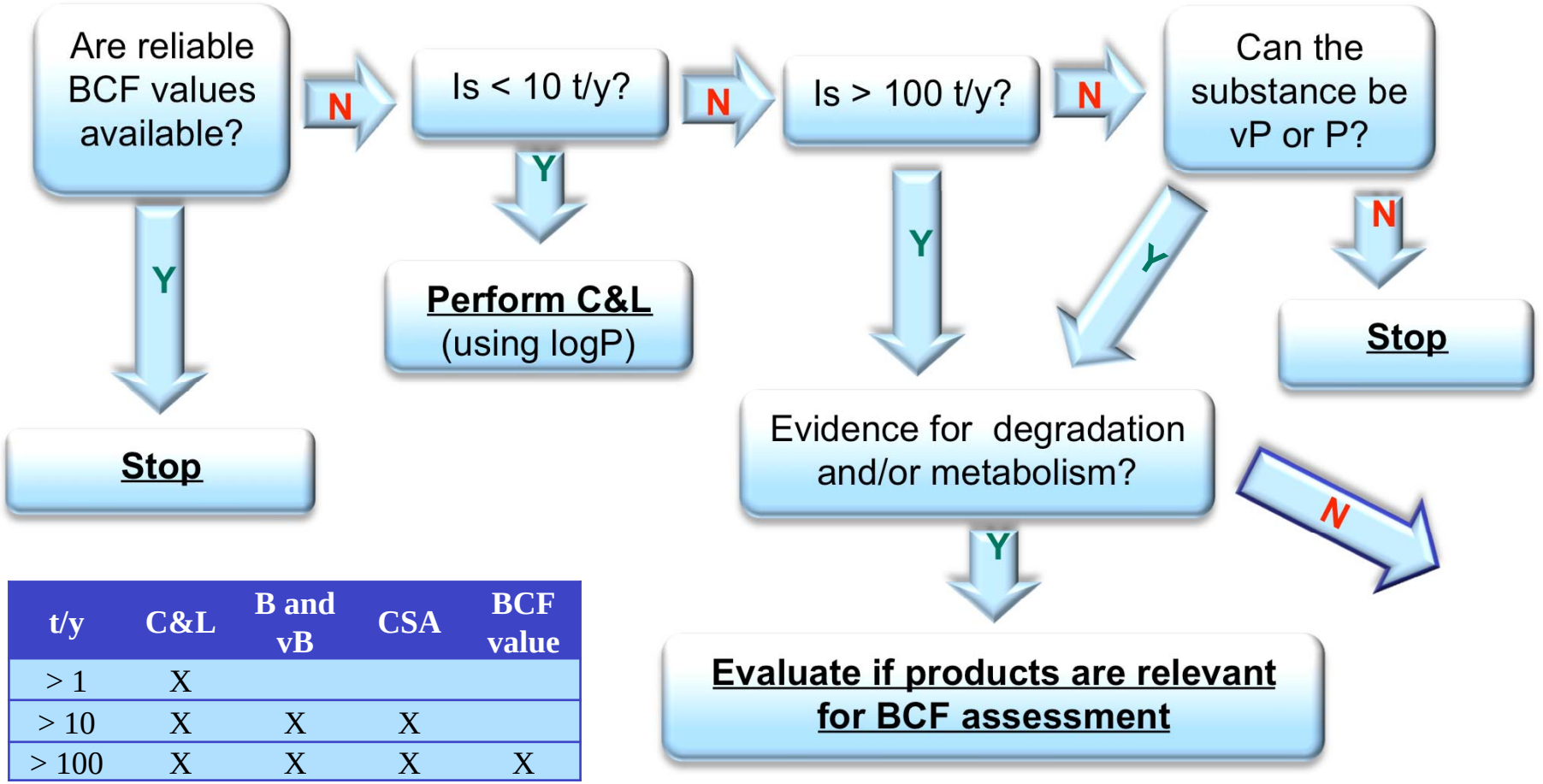
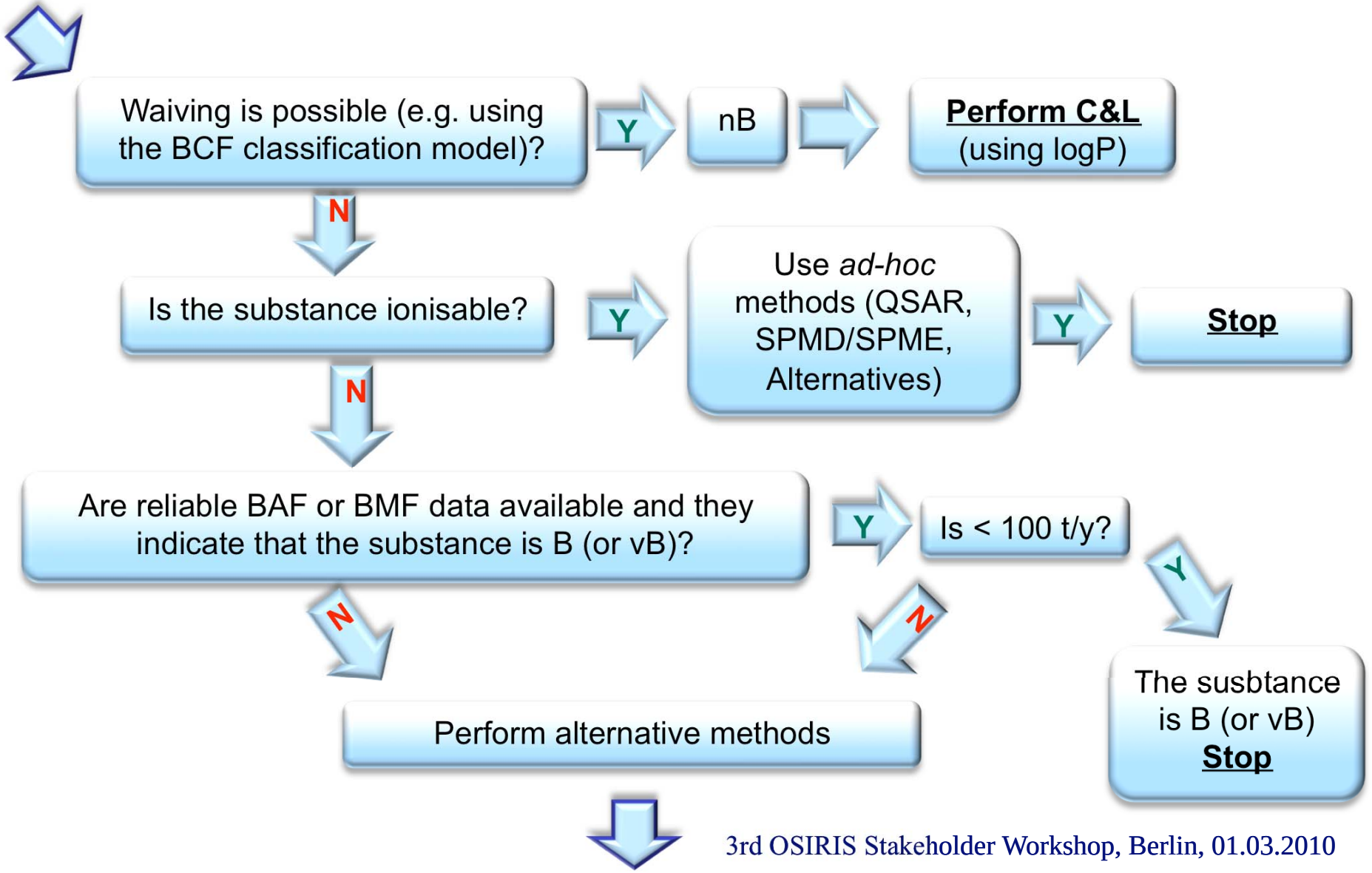
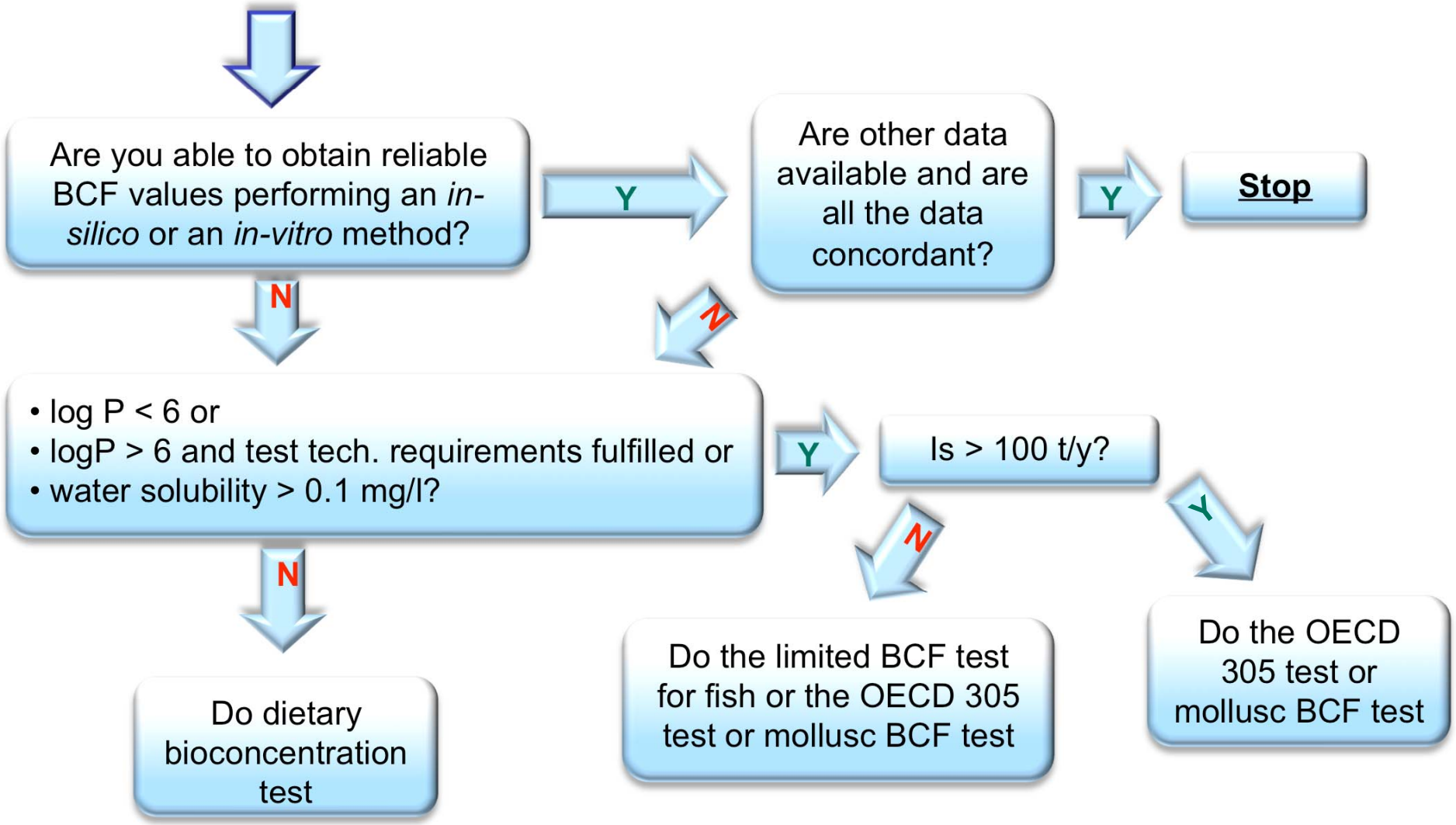
Conceptual scheme



t/y	C&L	B and vB	CSA	BCF value
> 1	X			
> 10	X	X	X	
> 100	X	X	X	X


Waiving is possible (e.g. using the BCF classification model)?
Y
nB
Perform C&L (using logP)
N
Is the substance ionisable?
Y
Use ad-hoc methods (QSAR, SPMD/SPME, Alternatives)
Y
Stop
N
Are reliable BAF or BMF data available and they indicate that the substance is B (or vB)?
Y
Is < 100 t/y?
Y
N
N
The susbtance is B (or vB) Stop
Perform alternative methods


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
N
• log P < 6 or
• logP > 6 and test tech. requirements fulfilled or
• water solubility > 0.1 mg/l?
Y
Is > 100 t/y?
N
Y
N
Do dietary bioconcentration test
Do the limited BCF test for fish or the OECD 305 test or mollusc BCF test
Do the OECD 305 test or mollusc BCF test

Uncertainty and combination of data

(example kindly provided by Universitat Rovira i Virgili – Tarragona)

1,2,3,4-tetrachloro-benzene

Data source	Reliability score	log BCF								
EURAS	2	3.2	3.2							
Arnot	1	3.0	3.0	3.4	3.4	3.4	3.4	3.4	3.6	3.8

Data source	Reliability weight	Basic probability assignments			
		m {nB}	m {B}	m {vB}	m {nB, B, vB} unknown
EURAS	0.47	0.50	0	0	0.50
Arnot	0.53	0.18	0.55	0.09	0.18

Data source	Basic probability assignments			
	m {nB}	m {B}	m {vB}	m {nB, B, vB} unknown
Combined	0.33	0.29	0.05	0.33

Uncertainty and combination of data

(example kindly provided by Universitat Rovira i Virgili – Tarragona)

	combined probability assignment (m_3)			*Readily*		*Not Readily*		length of belief–plausibility intervals				
name	*Readily*	*Not Readily*	*Readily, Not Readily*	[*Bel*	*Pl*]	[*Bel*	*Pl*]	Biowin5	CERI	Biowin5 ⊕ CERI	uncertainty reduction (%)	decision
chloromethane	0.47	0.21	0.32	0.47	0.79	0.21	0.53	0.4	0.6	0.32	20	*Uncertain*
2,4-dimethylphenol	0.84	0	0.16	**0.84**	1	0	0.16	0.4	0.4	0.16	60	*Readily*
3-chloro-1-propene	0.73	0.09	0.18	**0.73**	0.91	0.09	0.27	0.4	0.4	0.18	55	*Readily*
dichloromethane	0.375	0.375	0.25	0.38	0.63	0.38	0.63	0.4	0.4	0.25	38	*Uncertain*
2-nitropropane	0	0.95	0.05	0	0.05	**0.95**	1	0.08	0.6	0.05	38	*Not Readily*
2-methylbenzenamine	0.05	0.87	0.08	0.05	0.13	**0.87**	0.95	0.08	0.6	0.08	0	*Not Readily*
1,4-benzenediamine	0	0.97	0.03	0	0.03	**0.97**	1	0.08	0.4	0.03	63	*Not Readily*

Uncertainty Reduction in Environmental Data with Conflicting Information

A. Fernandez, R. Rallo, F. Giralt, *Environ. Sci. Technol.* ***2009, 43, 5001–5006***

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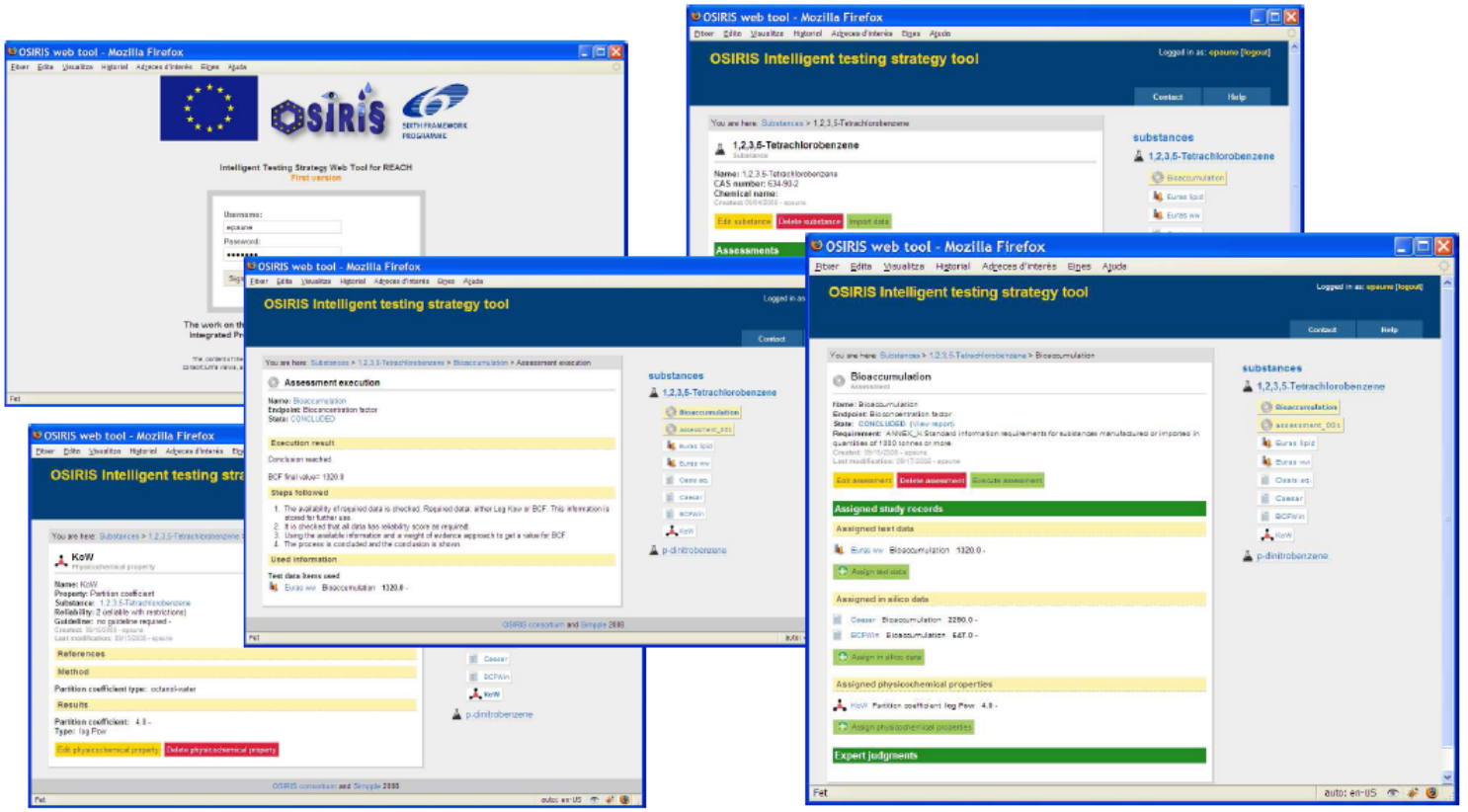
The webtool (developed by SIMPPLE)



http://osiris.simpple.com

simpple

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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.

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Thank you very much for your attention!

Questions?

Comments?