Chemical concentration, activity, fugacity, and toxicity

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Outline

- A refresher of some physical chemistry
- Four chemicals, log K_{OW} = 2, 4, 6, 8
- Two organisms, fish and mammal
- Bioaccumulation "experiments"
- Toxicity "experiments"
- Concluding thoughts
- Part II by Jon Arnot (Thursday am)

Some physical chemistry of organic liquid solutes in dilute solutions

Raoult	$P = x\,P^S{}_L$	(ideal)
Raoult	$P = x\,\gamma\,P^S{}_L$	(non-ideal)
Dalton	$P = y\,P_T$	

so $P = x\,\gamma\,P^S{}_L = y\,P_T$

Rigorous fugacity version

$$f = x\,\gamma\,f_R = y\,\phi\,P_T$$

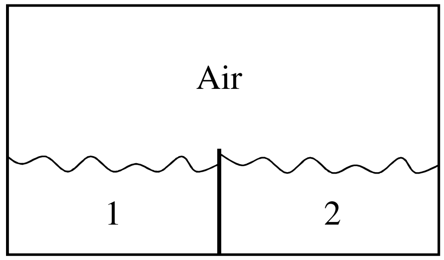
reduces to

$$P = x\,\gamma\,P^S{}_L = y\,P_T$$

when $f = P$, $f_R = P^S{}_L$, $\phi = 1$

f and P are "escaping pressures" Pa

Two immiscible liquids and a gas phase in equilibrium, liquid solute.



$$P \approx f = x_1\gamma_1 P^S{}_L = x_2\gamma_2 P^S{}_L = yP_T$$

$$x_1\gamma_1 = x_2\gamma_2 = yP_T / P^S{}_L = P / P^S{}_L = \text{activity}$$

Saturation or solubility occurs when activity=1.0

Solubility is a measure of the activity coeff.

Equilibrium criteria

P or f or activity

Partition coefficients K_{A1}, K_{A2}, K_{12}

can be expressed using x_1, x_2, y or C_1, C_2, C_A g/m^3

e.g., K_{AW}, K_{OW}, K_{OA}

Depend on γ_1, γ_2 and $P^S{}_L$

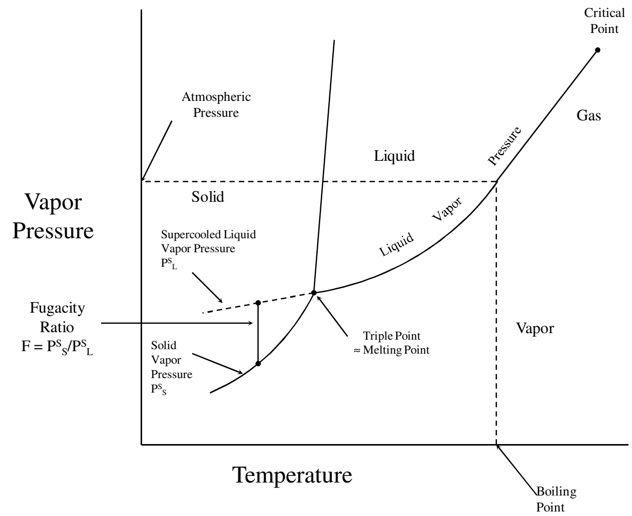
Can give ratios of γ_1 / γ_2

Relate C to f using C = Zf, Z is a “fugacity capacity”

Useful if solvent is complex, e.g., fish $Z = 1/(v\gamma P^S{}_L)$

$$C_{AIR} = Z_{AIR} f \quad C_1 = Z_1 f \quad C_2 = Z_2 f \quad K_{12} = Z_1/Z_2$$

What if the solute is solid or gaseous?



How do we treat solid or gaseous solutes?

The solute is in the liquid state and “thinks” it is a liquid so it behaves according to P^S_L

We must “correct” using F for solids

For gases we lump γP^S_L as H, Henry’s Law constant

If molar mass is large (and especially if the molecule is symmetrical)

Melting point is high i.e., >> 25°C

F is low, e.g., 0.1 to 0.001

$P^S_S << P^S_L$ $S^S_S << S^S_L$

$F = P^S_S / P^S_L = S^S_S / S^S_L$

Solubility x^S can be used to estimate γ

Liquids $x^S\gamma = 1$ Solids $x^S\gamma = F$

Be wary of reported P^S and S^S of solids!

QSARs and retention time methods give P^S_L and S^S_L

Four chemicals A, B, C and D

$\log K_{OW} = 2, 4, 6, 8$

Define MW, melting point, $\gamma_{octanol}$, vapor pressure

Deduce γ_{water}, solubility, K_{AW}, K_{OA} for both liquid and solid states

	Chemical			
Property	**A**	**B**	**C**	**D**
Log Kow	2	4	6	8
Molar mass g/mol	100	150	200	250
Molar volume cm3/mol	100	150	200	250
Meting point deg C	25	25	100	200
Fugacity ratio F	1	1	0.181	0.019
Liquid solubility g/m3	800	10	0.1	0.001
Solid solubility g/m3	800	10	0.018	1.85E-05
Liquid soly mol/m3	8	0.067	5.00E-04	4.00E-06
Solid soly mold/m3	8	0.067	9.05E-05	7.42E-08
Liquid soly in water mol frn	1.44E-04	1.20E-06	9.00E-09	7.20E-11
Liquid vapor pressure Pa	180	1	5.00E-03	3.00E-05
Solid vapor pressure Pa	180	1	9.05E-04	5.56E-07
Henry's const H Pa.m3/mol	22.5	15	10	7.5
Kaw ie H/RT	0.009	0.006	0.004	0.003
Liquid soly in air mol/m3	0.073	4.04E-04	2.02E-06	1.21E-08
Solid soly in air mol/m3	0.581	2.69E-05	1.83E-10	8.98E-16

	Chemical			
Property	**A**	**B**	**C**	**D**
Log Kow	2	4	6	8
Kow	1.00E+02	1.00E+04	1.00E+06	1.00E+08
Koa ie Kow/Kaw	1.10E+04	1.65E+06	2.48E+08	3.30E+10
Log Koa	4.04	6.22	8.39	10.52
Activity coeff in water	6.94E+03	8.33E+05	1.11E+08	1.39E+10
Activity coeff in octanol	9.92	11.90	15.87	19.84
Liquid soly in octanol g/m3	8.00E+04	1.00E+05	1.00E+05	1.00E+05
Solid soly in octanol g/m3	8.00E+04	1.00E+05	1.81E+04	1.85E+03
Liquid soly in octanol mol/m3	800	666.67	500	400
Solid soly in octanol mol/m3	800	666.67	90.53	7.42
Liquid soly in octanol mol frn	0.101	0.084	0.063	0.050
Z value in air	4.04E-04	4.04E-04	4.04E-04	4.04E-04
Z value in water	4.44E-02	6.67E-02	1.00E-01	1.33E-01
Z value in biota	5.07E-01	7.14E+01	1.07E+04	1.43E+06

Two organisms

100 g fish, 10% lipid

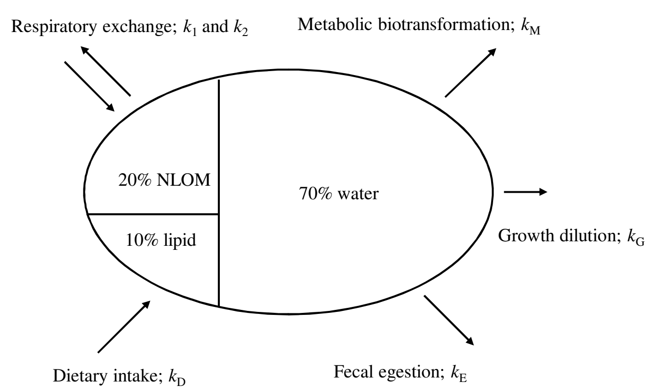
100 g mammal, 10% lipid

Respiration and feeding rates

lipid = octanol

No metabolic biotransformation

Two organisms – same properties and processes



NLOM equivalent to 3.5% lipid

Fish

Property	A	B	C	D
Fish volume m3	0.0001	0.0001	0.0001	0.0001
Fish mass kg	0.1	0.1	0.1	0.1
Respiration flow rate m3/day	0.05	0.05	0.05	0.05
Uptake efficiency water %	30	50	50	20
Rate constant k1 days-1	150	250	250	100
Rate constant k2 days-1	1.32E+01	2.33E-01	2.34E-03	9.35E-06
BCF (k_1/k_2)	1.14E+01	6.42E+02	6.42E+04	1.61E+07
Half time (respiration) days	5.27E-02	2.97E+00	2.97E+02	7.42E+04
Feeding rate kg/day	0.002	0.002	0.002	0.002
Absorption efficiency %	50	50	50	30
Dietary uptake rate constant days-1	0.01	0.01	0.01	0.006
Digestion factor Q	3	3	3	3
Egestion rate constant days-1	3.33E-03	3.33E-03	3.33E-03	2.00E-03
Half time (diet) days	2.08E+02	2.08E+02	2.08E+02	3.47E+02

Mammal

Property	A	B	C	D
Mammal volume m3	0.0001	0.0001	0.0001	0.0001
Mammal weight kg	0.1	0.1	0.1	0.1
Respiration flow rate m3/day	0.085	0.085	0.085	0.085
Uptake efficiency air%	70	70	70	50
Rate constant k1 days-1	595	595	595	425
Rate constant k2 days-1	4.74E-01	3.36E-03	2.24E-05	1.20E-07
BCF (k_1/k_2)	3.16E+02	4.46E+04	6.68E+06	1.25E+09
Half time (respiration) days	1.46E+00	2.06E+02	3.09E+04	5.76E+06
Feeding rate kg/day	0.002	0.002	0.002	0.002
Absorption efficiency %	80	80	80	60
Dietary uptake rate constant days-1	0.016	0.016	0.016	0.012
Digestion factor Q	30	30	30	30
Egestion rate constant days-1	5.33E-04	5.33E-04	5.33E-04	4.00E-04
Half time (diet) days	1.30E+03	1.30E+03	1.30E+03	1.73E+03

Bioconcentration "experiment"

$C_{Water} = 1\ \mu g.m^{-3}$ of each chemical

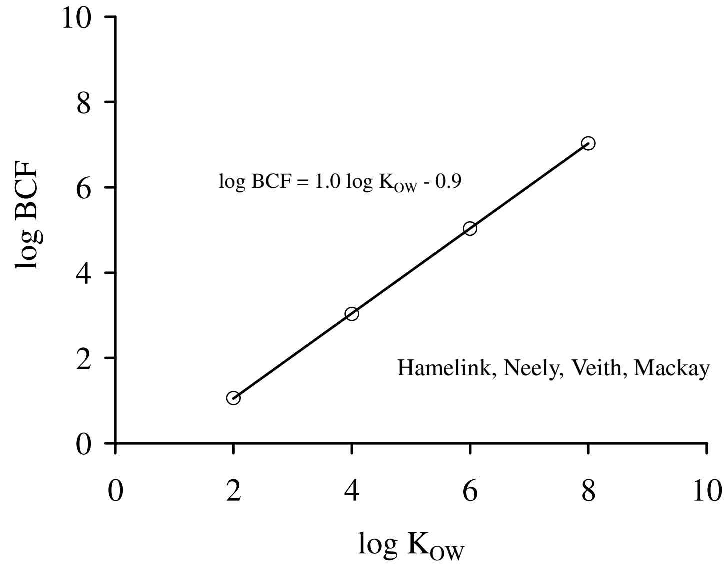
air is in equilibrium, so

$C_{Air} = 0.009$ to $0.003\ \mu g.m^{-3}$ depending on K_{AW}

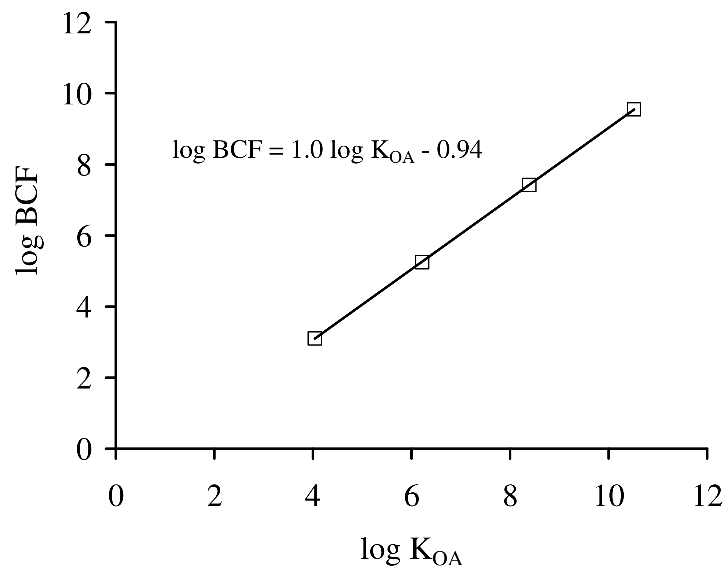
Bioconcentration "experiment"

Fish	**A**	**B**	**C**	**D**
Concn in water ug/m3	1	1	1	1
Concn in water mol/m3	1.00E-08	6.67E-09	5.00E-09	4.00E-09
Fugacity in water and fish Pa	2.25E-07	1.00E-07	5.00E-08	3.00E-08
Activity in water and fish	1.25E-09	1.00E-07	1.00E-05	1.00E-03
Concn in fish ug/m3	1.14E+01	1.07E+03	1.07E+05	1.07E+07
BCF (fish/water)	1.14E+01	1.07E+03	1.07E+05	1.07E+07
Half time (respiration) days	5.27E-02	2.97E+00	2.97E+02	7.42E+04
Mammal	**A**	**B**	**C**	**D**
Concn in air ug/m3	9.08E-03	6.05E-03	4.04E-03	3.03E-03
Partial pressure or fugacity Pa	2.25E-07	1.00E-07	5.00E-08	3.00E-08
Activity in air and mammal	1.25E-09	1.00E-07	1.00E-05	1.00E-03
Concn in mammal ug/m3	1.14E+01	1.07E+03	1.07E+05	1.07E+07
BCF (mammal/air)	1.26E+03	1.77E+05	2.65E+07	3.53E+09
Half time (respiration) days	1.46E+00	2.06E+02	3.09E+04	5.76E+06

Fish BCF ≈ 0.1 K_{OW} ≈ $L.K_{OW}$



Mammal BCF ≈ $L.K_{OW}/K_{AW}$ ≈ $L.K_{OA}$



Why is the empirical slope < 1?

1. Insufficient time for equilibration ?
2. Bioavailability ?
3. K_{OW} overestimated by QSARs ?
4. Water and NLOM partitioning at low K_{OW} ?
5. Lipid ≠ Octanol ?
6. Biotransformation and growth ?
7. Other ?

Toxicity "experiment"

Assume toxic effect at 3 $mmol.kg^{-1}$ or 3 $mol.m^{-3}$

i.e. narcosis

What are the water and air concentrations required to cause toxicity?

Essentially a "backward" bioconcentration experiment

Fish	A	B	C	D
Conc in fish mol/m3 or mmol/kg	3	3	3	3
Concn in water mol/m3	2.63E-01	2.80E-03	2.80E-05	2.80E-07
Concn in water g/m3	2.63E+01	4.20E-01	5.61E-03	7.01E-05
Ratio Cw/solid solubility	0.033	0.042	0.310	3.779
Fugacity in water and fish Pa	5.92E+00	4.20E-02	2.80E-04	2.10E-06
Activity in water and fish	0.033	0.042	0.056	0.070

Mammal	A	B	C	D
Conc in org mol/m3 or mmol/kg	3	3	3	3
Concn in air mol/m3	2.39E-03	1.70E-05	1.13E-07	8.49E-10
Part press in air Pa	5.92E+00	4.20E-02	2.80E-04	2.10E-06
Concn in air g/m3	2.39E-01	2.54E-03	2.26E-05	2.12E-07
Ratio part-pres/solid vapor press	0.033	0.042	0.310	3.779
Ratio part-pres/liquid vapor press	0.033	0.042	0.056	0.070
Fug and pp in air and org Pa	5.92E+00	4.20E-02	2.80E-04	2.10E-06
Activity in air and org	0.033	0.042	0.056	0.070

Concentration vs activity vs fugacity

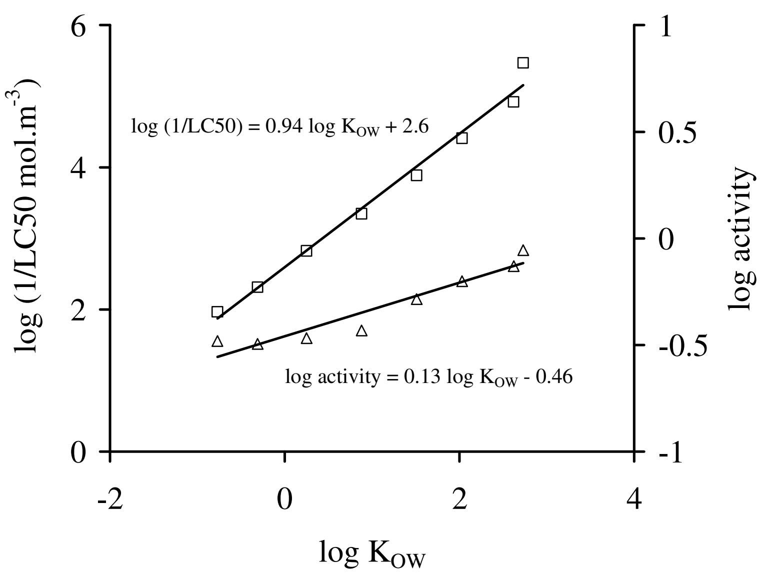
Concentrations and fugacities vary by about six orders of magnitude

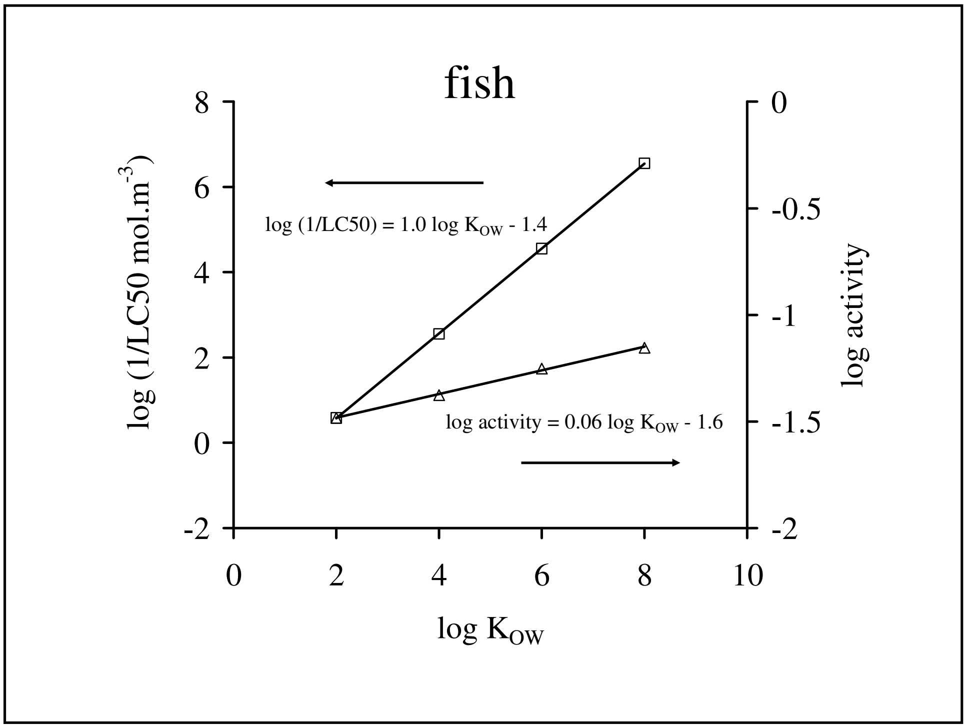
Activities vary relatively little (factor of 3)

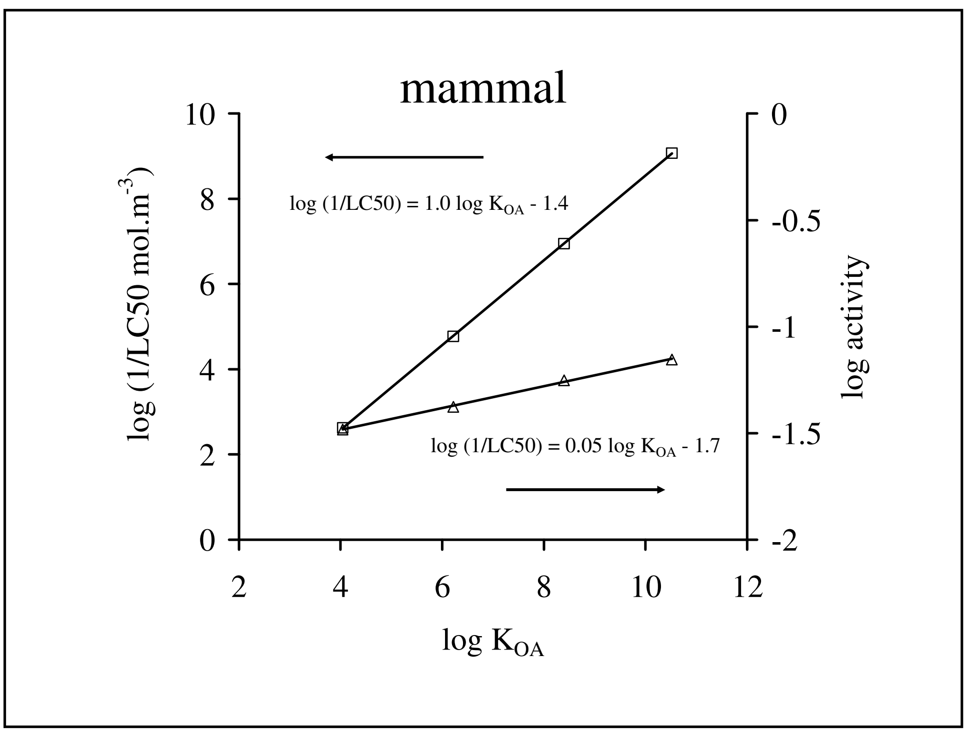
The system is striving for equi-fugacity, externally and internally.

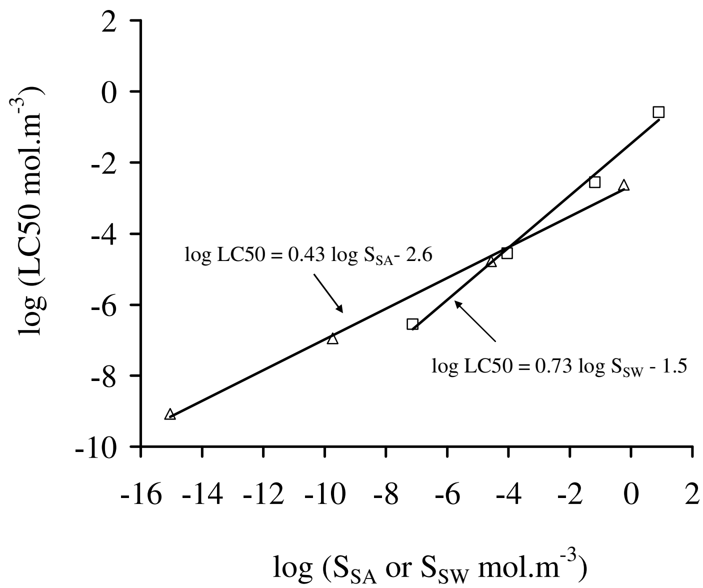
Data compiled by Ferguson 1939

	Sea urchin eggs		Tadpole		*B. typhosus*		Red spider		Ox blood	
Alcohol	**mol.L^{-1}**	**activity**	**mol.L^{-1}**	**activity**	**mol.L^{-1}**	**activity**	**mol.L^{-1}**	**activity**	**mol.L^{-1}**	**activity**
Methanol	0.719	0.019	0.57	0.014	10.8	0.33	1.7×10^{-4}	0.26	7.34	0.22
Ethanol	0.408	0.026	0.29	0.020	4.86	0.32	1.0×10^{-4}	0.32	3.24	0.22
Propanol	0.136	0.034	0.11	0.029	1.5	0.34	4.7×10^{-5}	0.42	1.08	0.24
Butanol	0.0454	0.043	0.038	0.038	0.45	0.37	1.7×10^{-5}	0.47	0.318	0.27
Pentanol	0.0240	0.070	-	-	0.13	0.52	8.1×10^{-6}	0.56	0.091	0.31
Hexanol	-	-	-	-	0.039	0.63	-	-	-	-
Heptanol	17.2×10^{-4}	0.112	-	-	0.012	0.74	-	-	0.012	0.77
Octanol	5.10×10^{-4}	0.113	-	-	3.4×10^{-3}	0.88	-	-	4.0×10^{-3}	0.87

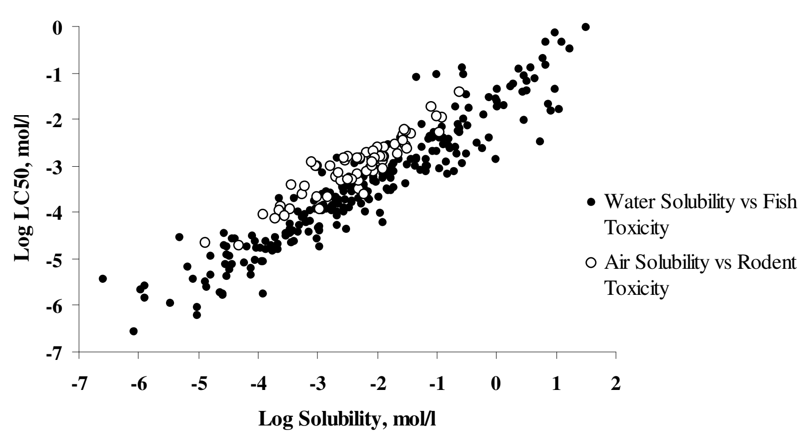



fish
log (1/LC50 mol.m-3)
log activity
log (1/LC50) = 1.0 log KOW - 1.4
log activity = 0.06 log KOW - 1.6
log KOW
8
6
4
2
0
-2
0
-0.5
-1
-1.5
-2
0
2
4
6
8
10


mammal
log (1/LC50 mol.m-3)
log activity
log (1/LC50) = 1.0 log KOA - 1.4
log (1/LC50) = 0.05 log KOA - 1.7
log KOA
10
8
6
4
2
0
0
-0.5
-1
-1.5
-2
2
4
6
8
10
12



Courtesy Gilman Veith, Larry Brooke, and Ken Wallace...



Some conclusions and points for discussion

- Bioconcentration in fish from water and mammals from air is well understood using K_{OW} and K_{OA}
- Narcosis is well characterized by 3 mol.m^{-3} ± factor of 2
- Uptake times can be long and can exceed short term test duration
- Solubility of solids can limit partitioning and toxicity
- Don't use exposure concentrations > solubility: meaningless results!
- Biotransformation, dynamics and growth are important.
- Challenges of "selective" toxics: we have to get the "simple" narcosis model right first. Then we use this as a basis for developing more rational and effective methods of modeling toxicity of more challenging substances and eliminating **unnecessary** (but not all) animal testing.

QSARs and 5 D's

Toxicity depends on:

1. **Delivery** to organism, i.e., Corg/Cenv
2. **Distribution** in organism (toxicokinetics)
3. **Disruption** (biochemical)
4. **Dynamics** and efficiency of uptake
5. **Degradation** of chemical in organism (biotransformation)

   as well as K_{OW}

Is a general QSAR for toxicity attempting too much? Categories?

Perhaps a set of QSARs yielding parameters that can be combined using a model?

Thank you!