Chemical concentration, activity, fugacity, and toxicity: dynamic implications

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Overview

- Building on Part I by Don Mackay
  - Four chemicals, log K_{OW} = 2, 4, 6, 8
  - Two organisms, fish and mammal
- Objectives
  - Reference point for acute "baseline" toxicity (narcosis)
  - Data quality
- Assumptions vs reality
  - Dynamic profiles and "complicating" factors (biotransformation rates, absorption efficiency)
- Internal vs external concentrations and activities

Reference point for hazard identification

- Lethality is "well defined"
- Toxic Ratio (TR) or "excess toxicity" = CBR_X (mmol.kg^{-1}) / CBR_N (mmol.kg^{-1})

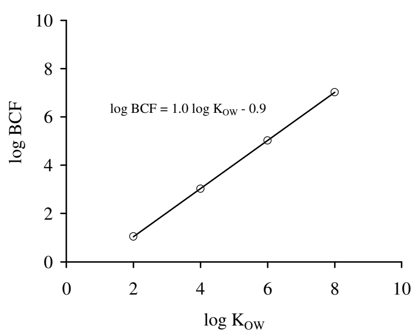
- If CBR_N = 3 mmol.kg^{-1} and TR > ~10 then chemical "x" has greater "potency"

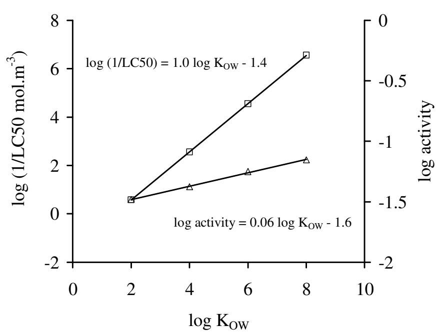
Equilibrium partitioning (EqP)

EqP = activity in exposure medium = activity in organism

Complete bioavailability

No biotransformation or growth dilution

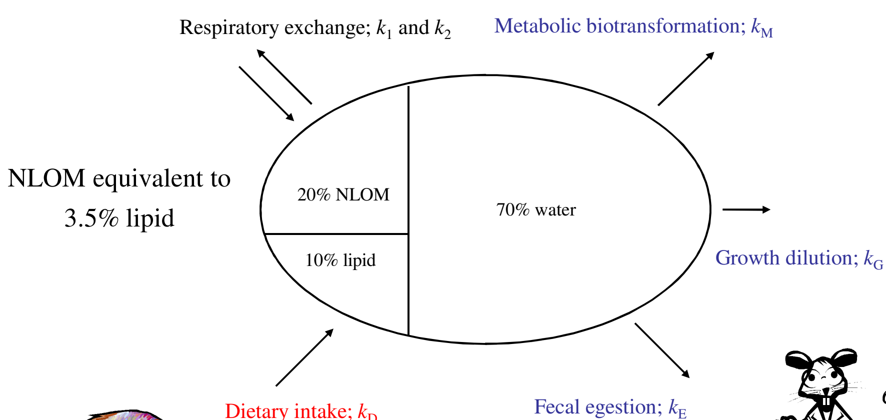


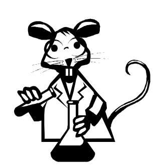


Series of toxicity “experiments”

- Illustrations using a kinetic mass balance model
    1. Fish
    2. Mammal
- Exposure concentrations based on EqP assumptions to exert a toxic effect at 3 mmol.kg^{-1} or 3 mol.m^{-3} whole body concentration, i.e., narcosis
- Four chemicals, each with three different metabolic biotransformation rates (0, 0.1, 1.0 d^{-1})

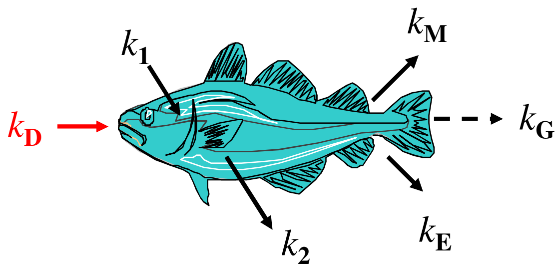
Two organisms – same properties and processes (air vs water)



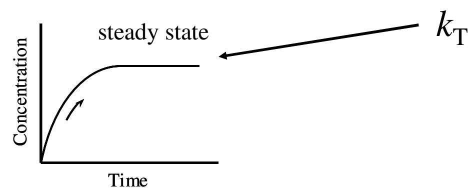


(both 100 g)

Model



$$C_B = ((k_1 \bullet C_{WD}) + (k_D \bullet C_D)) / \underbrace{(k_2 + k_E + k_M + k_G)}_{}$$



Equilibrium partitioning: fish

Chemical

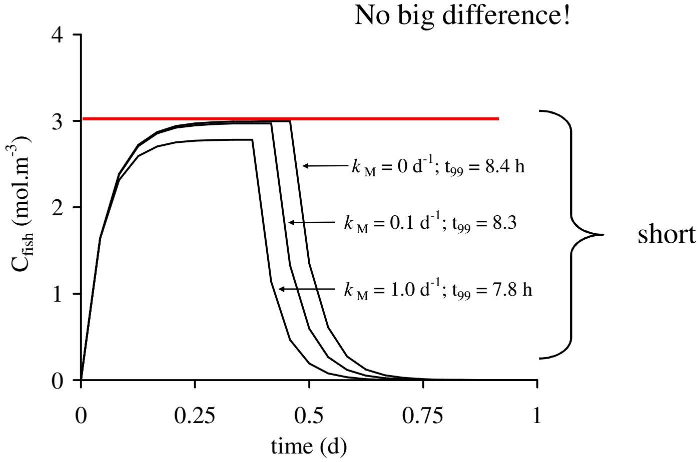
	A	B	C	D
Log Kow	2	4	6	8
Concn in fish mol/m3 or mmol/kg	3	3	3	3
BCF (fish/water)	1.14E+01	1.07E+03	1.07E+05	1.07E+07
Concn in water mol/m3	2.63E-01	2.80E-03	2.80E-05	2.80E-07
Concn in water g/m3	2.63E+01	4.20E-01	5.61E-03	7.01E-05
Activity in water and fish	0.033	0.042	0.056	0.070

Chemical A

C_{water} = 0.263 mol.m^{-3}

activity in fish ≈ activity in water ≈ 0.03

No big difference!

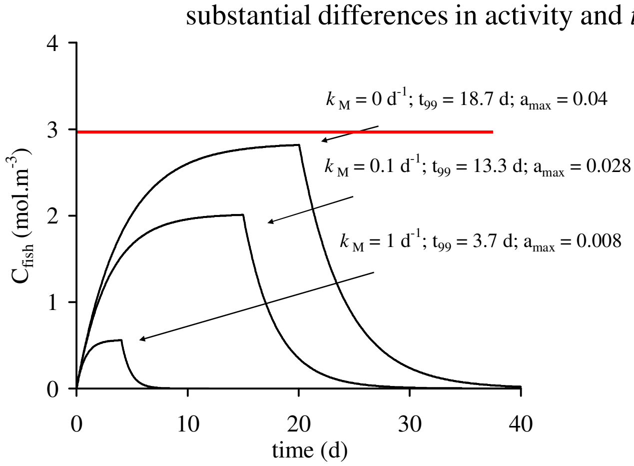


Chemical B

C_{water} = 0.0028 mol.m^{-3}

a_{water} = 0.04

substantial differences in activity and $t_{steady\ state}$



Chemical B

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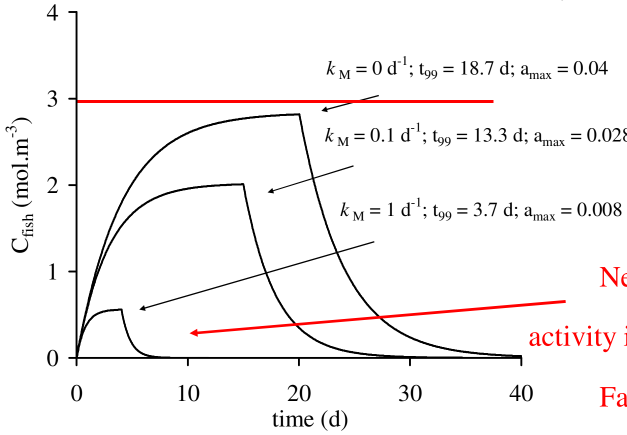


Need to increase C_{water} !!

activity in fish ≠ activity in water!!

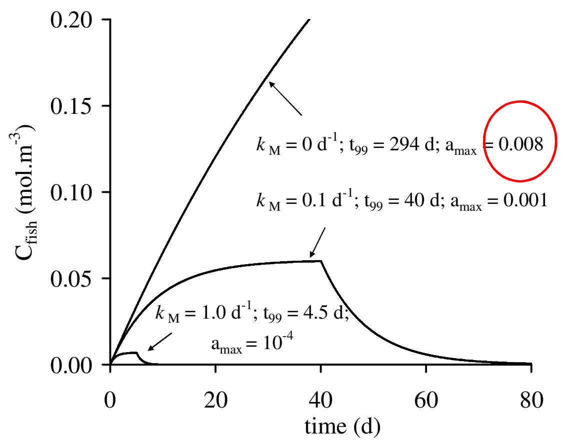
Factor of 5; a_{water} ~ 0.2

Chemical C

C_{water} = 0.028 mmol.m^{-3}

a_{water} = 0.056

big differences in activity and $t_{steady\ state}$



Chemical C

C_{water} = 0.028 mmol.m^{-3}

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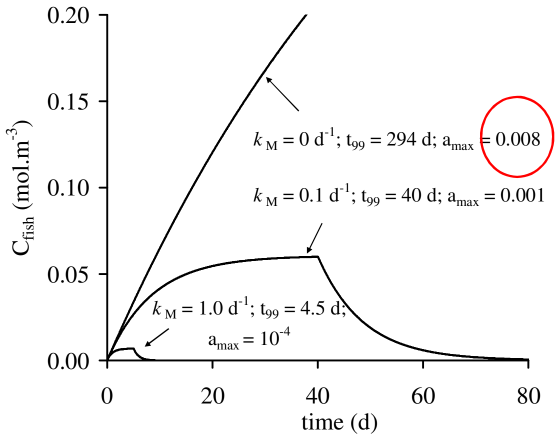
big differences in activity and $t_{steady\ state}$



Need to increase C_{water} !!
BUT, exceed water
solubility limits

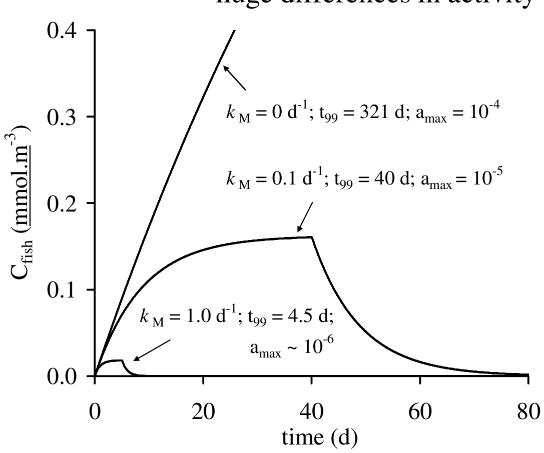
i.e., $a_{water} > 1$ X

Chemical D

$C^S_S = C_{water}$ = 0.074 μmol.m^{-3}

a_{water} = 0.07

huge differences in activity and $t_{steady\ state}$

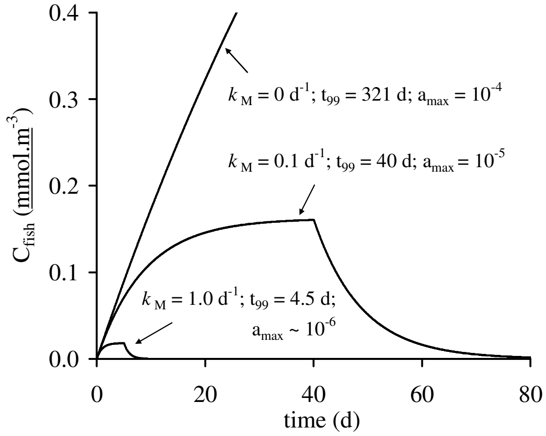


Chemical D

$C^S_S = C_{water} = 0.074\ \mu mol.m^{-3}$

$a_{water} = 0.07$

huge differences in activity and $t_{steady\ state}$

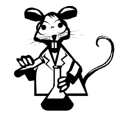


No chance!

Equilibrium partitioning: mammal

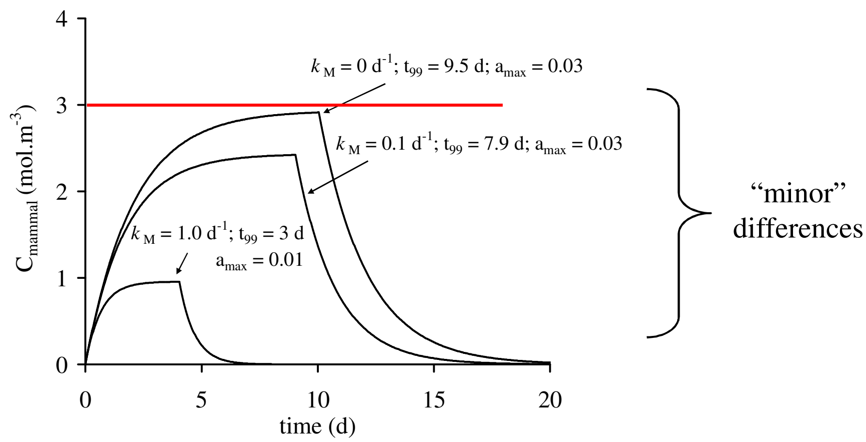
	Chemical			
	A	**B**	**C**	**D**
Log Kow	2	4	6	8
Concn in mammal mol/m3 or mmol/kg	3	3	3	3
BCF (mammal/air)	1.26E+03	1.77E+05	2.65E+07	3.53E+09
Concn in air mol/m3	2.39E-03	1.70E-05	1.13E-07	8.49E-10
Concn in air g/m3	2.39E-01	2.54E-03	2.26E-05	2.12E-07
Activity in air and mammal	0.033	0.042	0.056	0.070

Chemical A

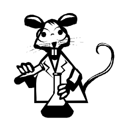


C_{air} = 0.0024 mol.m^{-3} a_{air} = 0.03

Lower concentrations in air compared to water

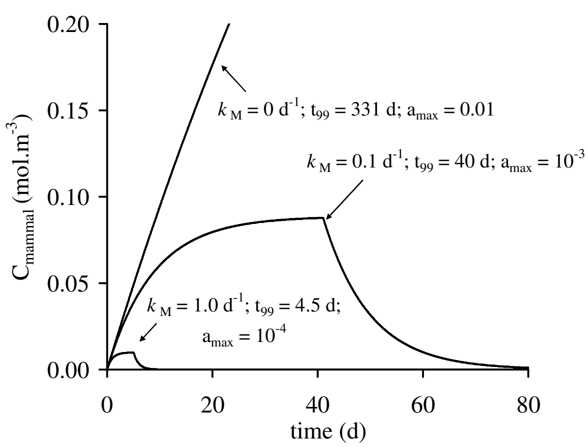


Chemical B

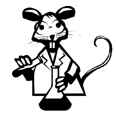


C_{air} = 0.017 mmol.m^{-3}

a_{air} = 0.04

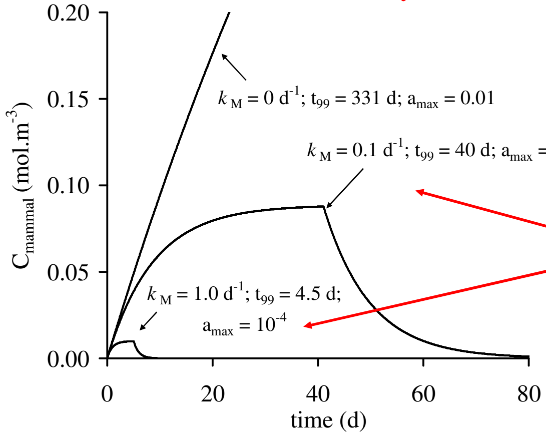


Chemical B



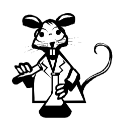
$C_{air} = 0.017\ mmol.m^{-3}$
$a_{air} = 0.04$

Maximum activity in mammal ≠ activity in air!!



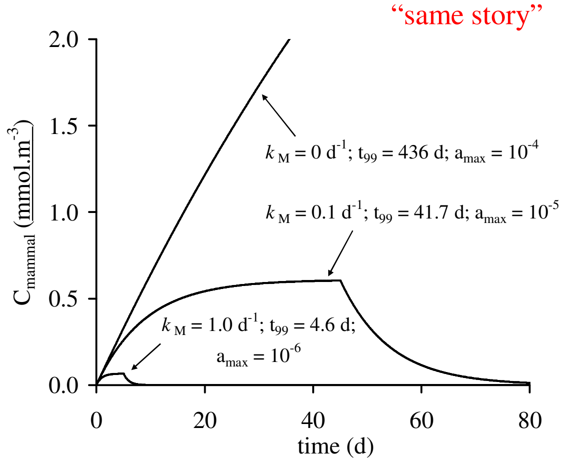
Need to increase C_{air} !!
BUT, exceed air
solubility limits, i.e.,
vapor pressure

Chemical C



$C_{air} = 0.11\ \mu mol.m^{-3}$
$a_{air} = 0.056$

"same story"

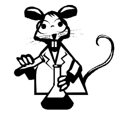


~ 560x

~ 5,600x

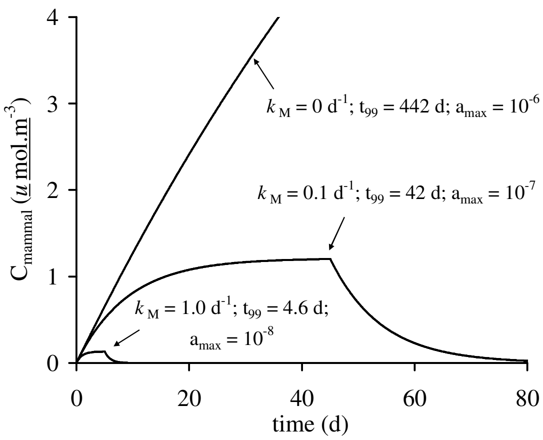
~ 56,000x

Chemical D



$P^S_S = C_{air} = 0.22$ nmol.m^{-3}

$a_{air} = 0.07$



“same story”

A view to a kill (96 h LD_{50})

Chemical C; fed 2x/d

Organism	Parameter	Units	k_M 0 d^{-1}	0.1 d^{-1}	1 d^{-1}
Fish	C_D	(mg/kg)	165,000	200,000	580,000
Fish	t_{99}	(d)	294	40	4.5
Mammal	C_D	(mg/kg)	102,000	124,000	360,000
Mammal	t_{99}	(d)	436	42	4.6

Inhalation exposure is assumed “irrelevant”

not at steady state or equilibrium!

BMFs are larger in the mammal

A view to a kill (96 h lethal dose)

Chemical C; but 0.5 * E_D

			k_M		
Organism	**Parameter**	**Units**	**0 d^{-1}**	**0.1 d^{-1}**	**1 d^{-1}**
Fish	C_D	(mg/kg)	330,000	400,000	X
Fish	t_{99}	(d)	294	40	4.5
Mammal	C_D	(mg/kg)	204,000	248,000	720,000
Mammal	t_{99}	(d)	436	42	4.6

Have to double the dose!

Summary

- Uptake times can be long and can exceed standard test durations, combined exposure routes may be necessary
- Exposure concentrations and activities “rarely” approximate internal concentrations and activities
- Metabolites that may be toxic will further complicate interpretation of toxicity measurements
- Need to measure both internal and external concentrations to identify “more potent” chemical
- Need for a quality toxicity dataset
- Uncertain data result in uncertain models

Ferguson 1939

Careful inspection of the toxicity data can support Ferguson's proposal that activity be used to interpret toxicity data such that "the disturbing effect of phase distribution is eliminated from the comparison of toxicities"

Thank you!