Predicting Chemical Partitioning and Toxicity Using Molecular Interaction Models:

The End of the Age of Octanol

Dominic M. Di Toro

Edward C. Davis Professor of Civil and Environmental Engineering
University of Delaware, Newark, DE

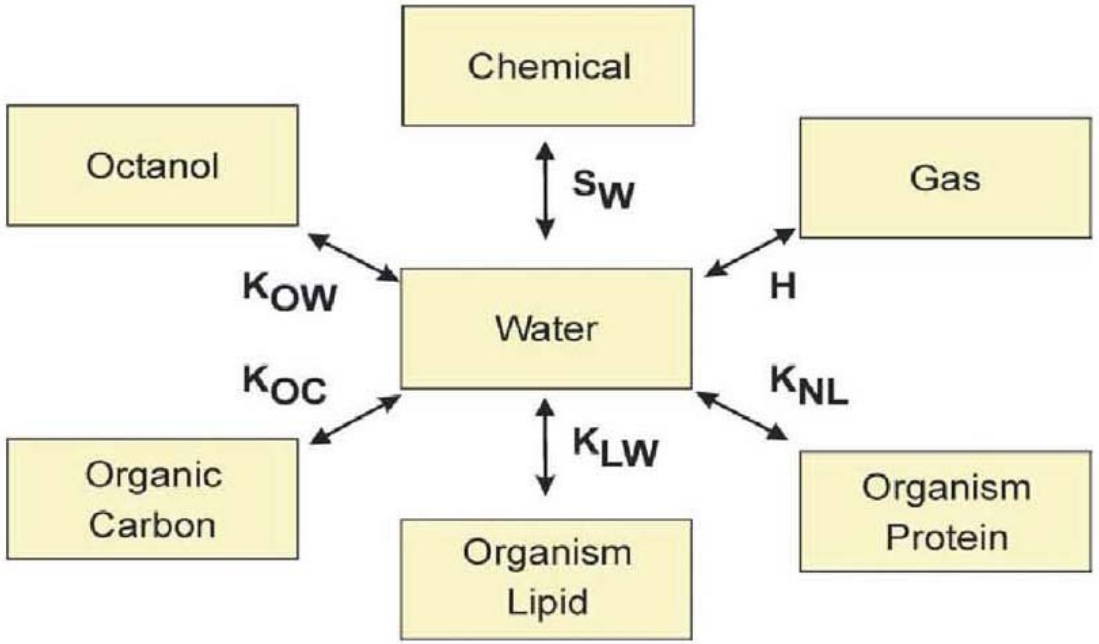
University of Houston
Department of Civil and Environmental Engineering's
Beyer Distinguished Lecture Series
April 18, 2012

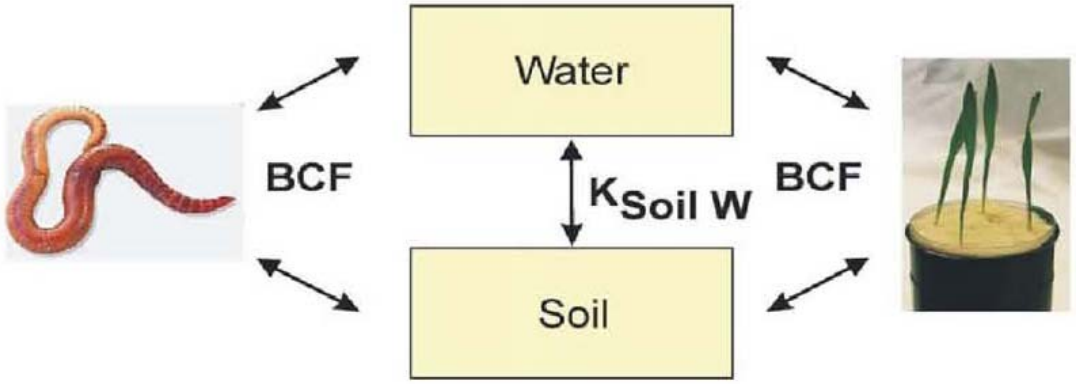
The Problem
- Predict Partition Coefficients -

Physical Chemistry

Environmental Chemistry

Environmental Modeling





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There is Nothing so Practical
as a
Good Theory

...Kurt Lewin

All Models are Wrong

Some Models are Useful

...George Box

It is **Theory** that Decides
What We Can **Observe**

...Albert Einstein

We are Perhaps **Not Far Removed**
From the **Time** when
We shall be able to Submit
the **Bulk** of Chemical Phenomena
to **Calculation**

...Joseph Louis Gay-Lussac, 1808

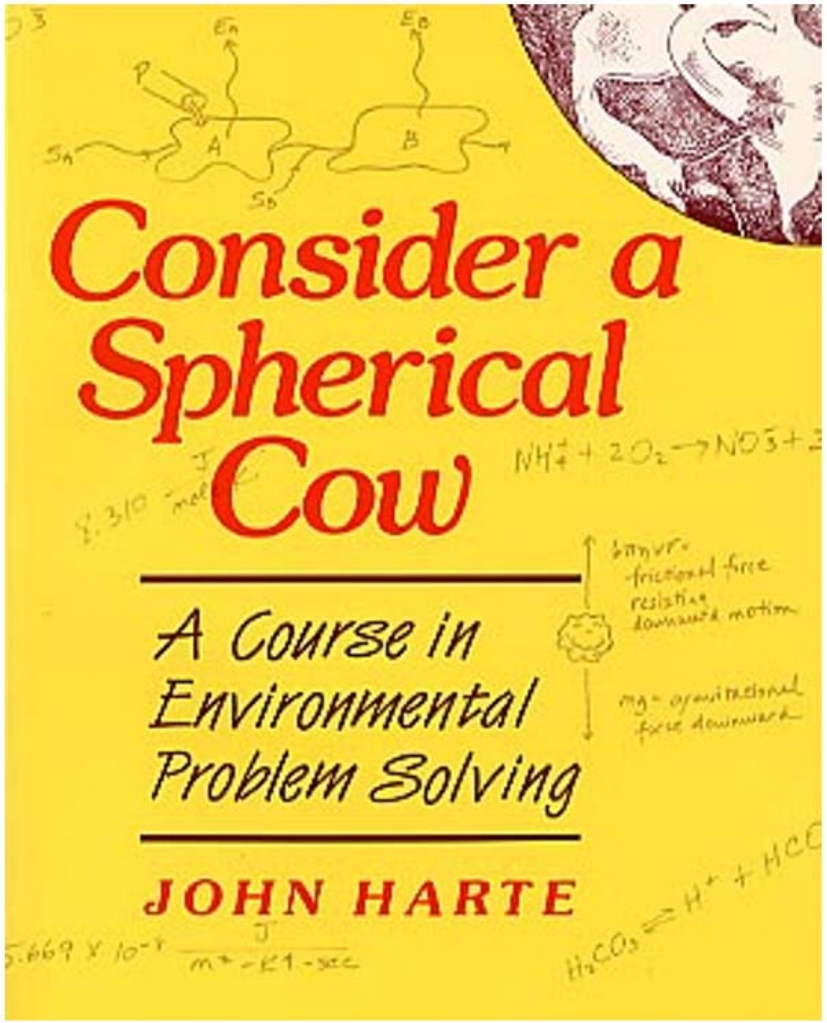
Every Attempt to Employ
Mathematical Methods
in the Study of **Chemical Questions**
Must be Considered
Profoundly Irrational

...Auguste Comte, Cours de Philosophie Positive, 1830

The Physical Laws necessary
for the **Mathematical** Theory of
a **Large Part** of **Physics** and
the ***Whole*** of **Chemistry**
are thus **Completely Known**

...P.A.M. Dirac, Proc. Royal Society, 1929

Simplifications are difficult to justify…



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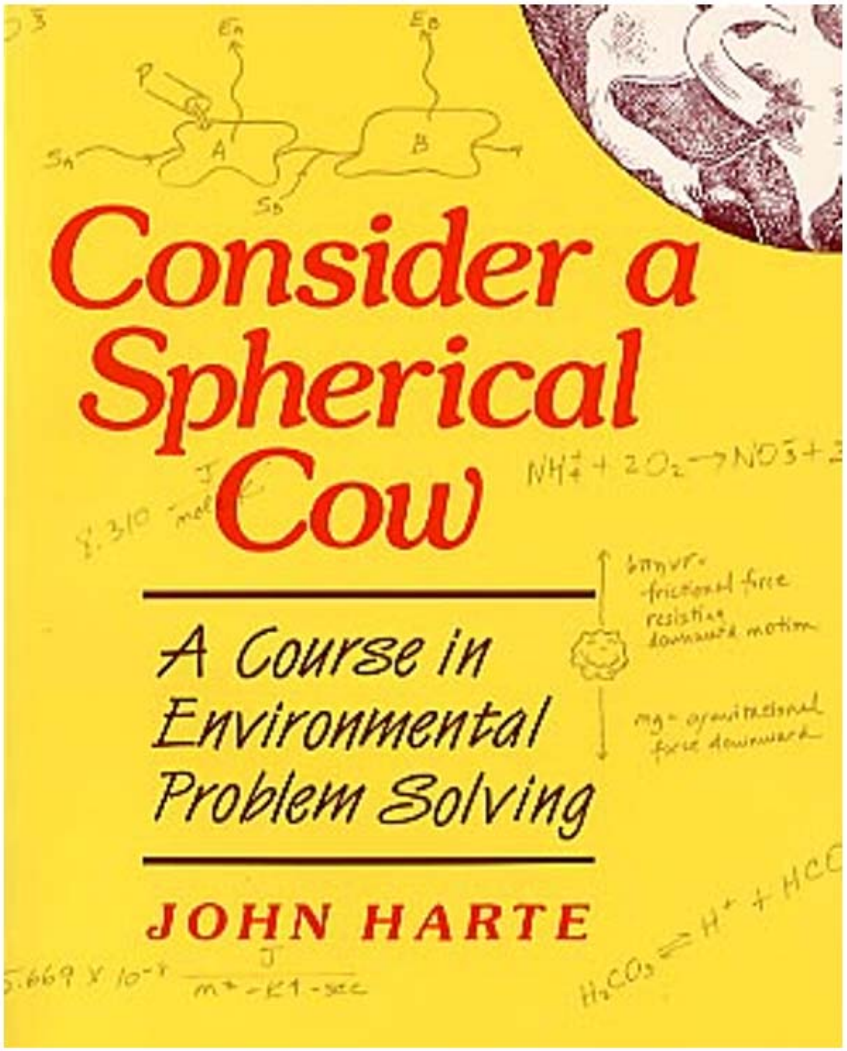
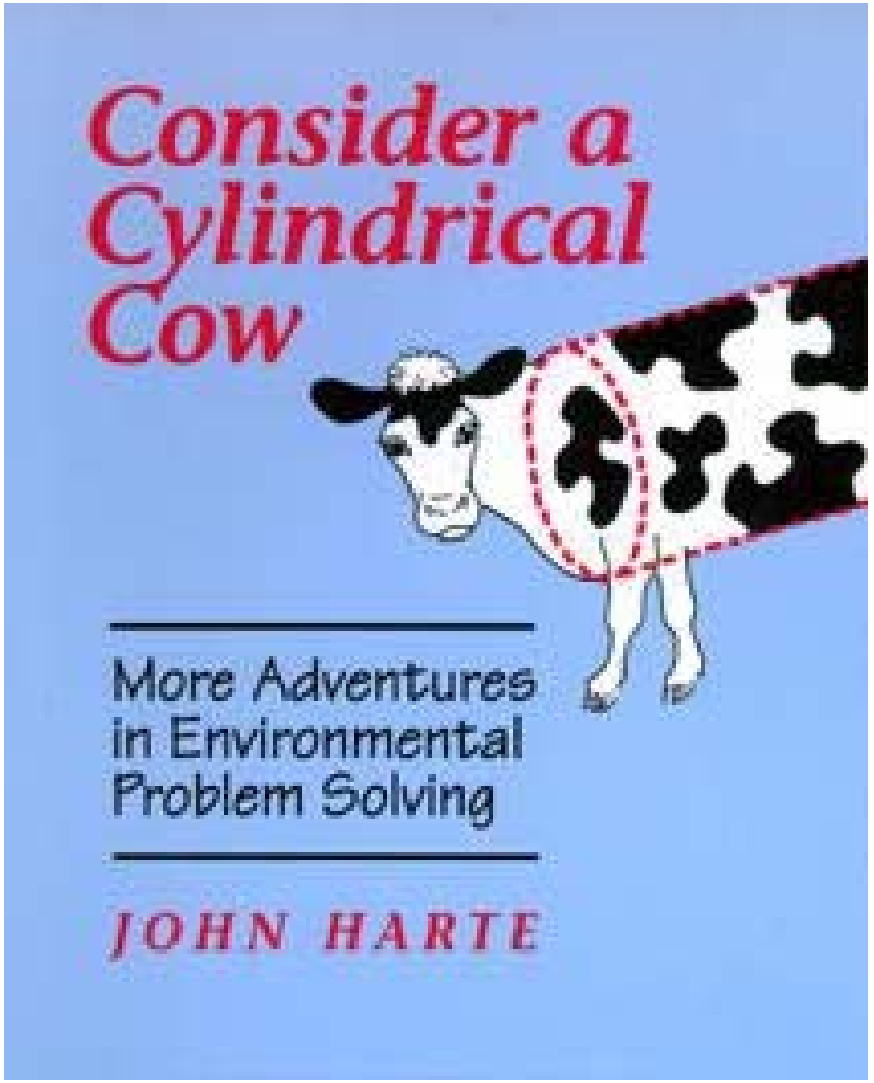
...Or Improve...





The Age of Octanol
- Partitioning -

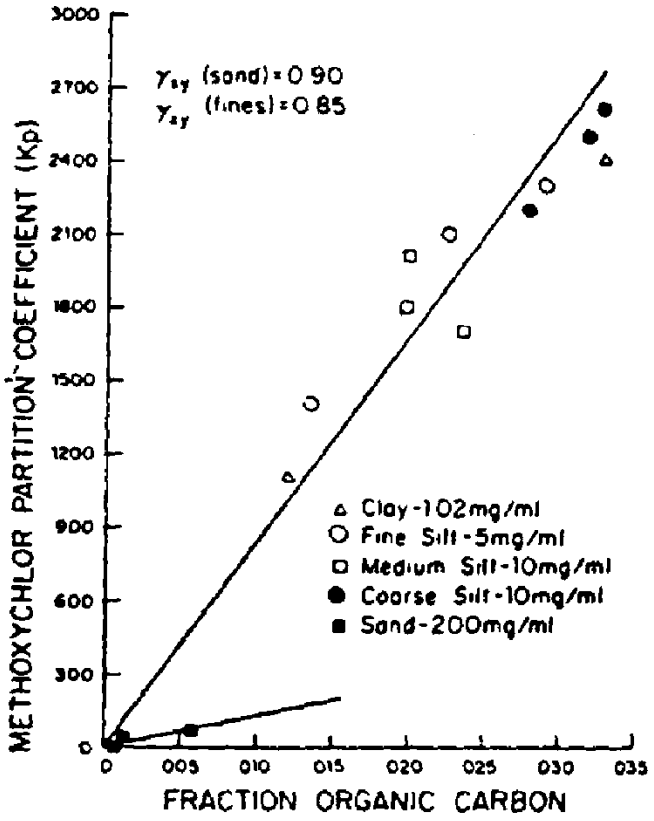
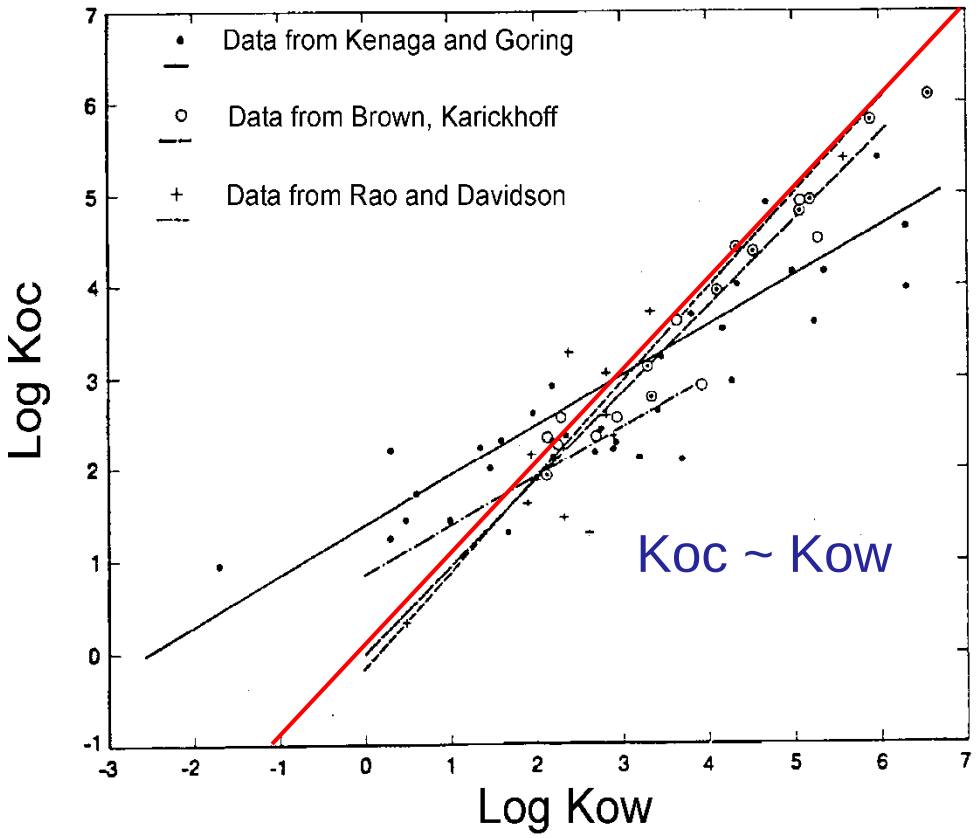


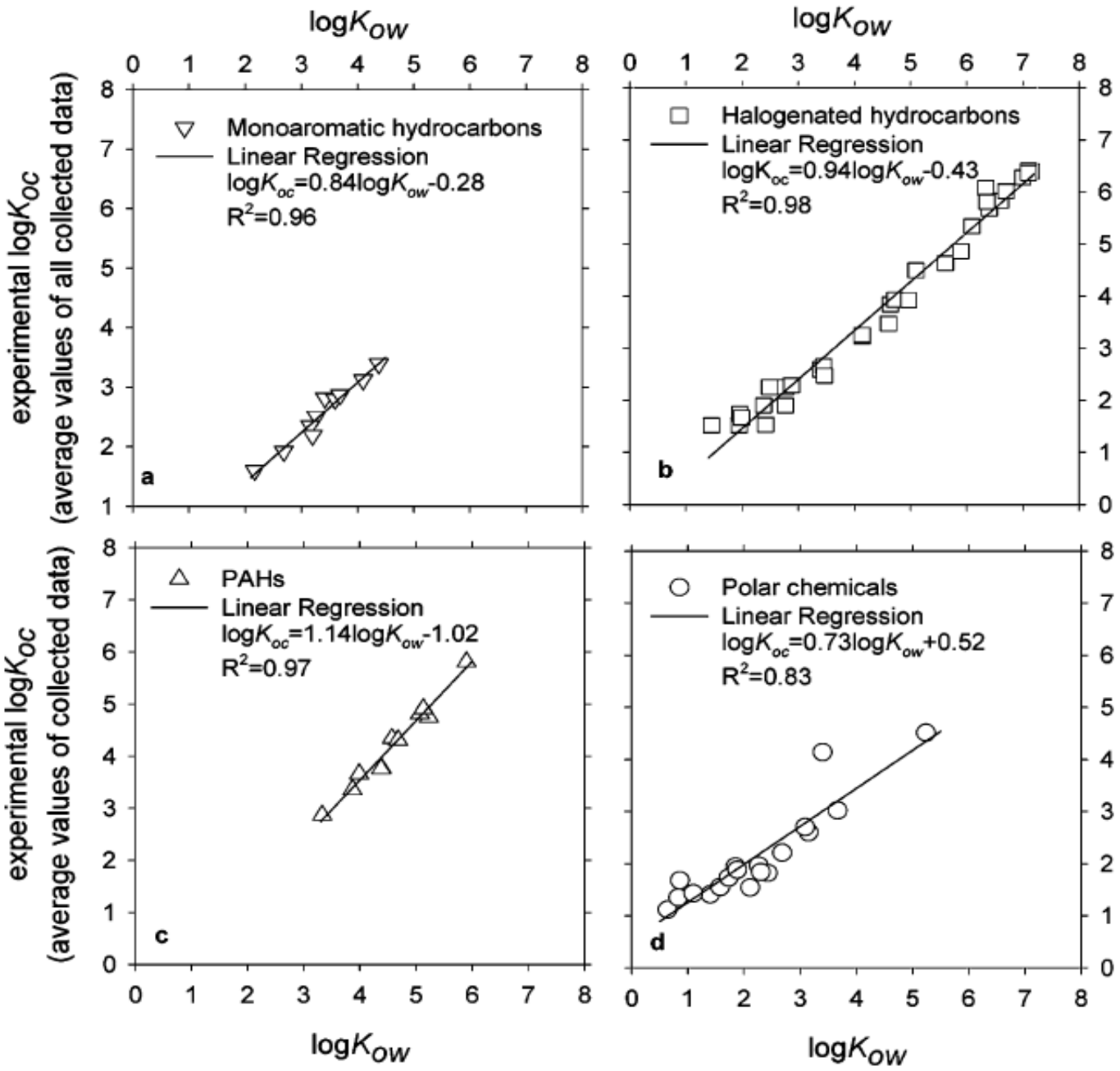
Fig. 4. Methoxychlor K_p as a function of sediment organic carbon.



Lyman, W. J., Reehl, W. F., & Rosenblatt, D. H. (1982). Handbook of Chemical Property Estimation Meth
McGraw-Hill Book Co.

Karickhoff, S. W., Brown, D. S., & Scott, T. A. (1979). Sorption of hydrophobic pollutants on natural sediments. Wat. Res, 13, 241-248.

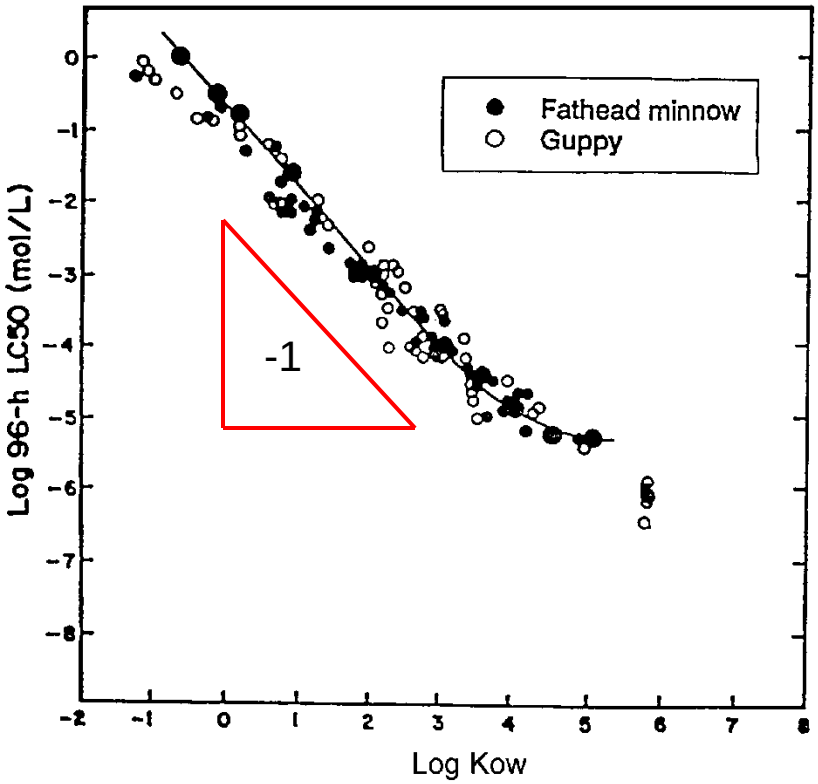
Log K_{OC} - K_{OW} Regressions



Nguyen TH, Goss K-U, Ball WP. 2005. Environ Sci Technol 39:913-924.

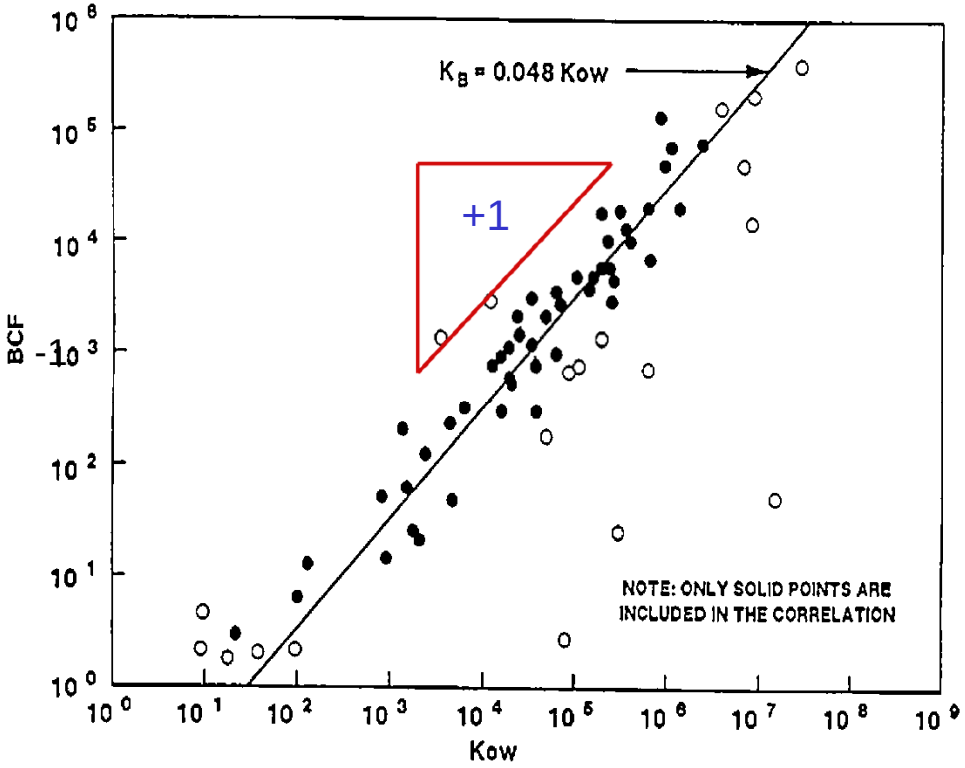
The Age of Octanol
- Bioaccumulation & Toxicity -

CBB = BCF x LC50



Veith, G.D. et al., Can. J. Fish. Aquat. Sci., Vol. 40, 1983

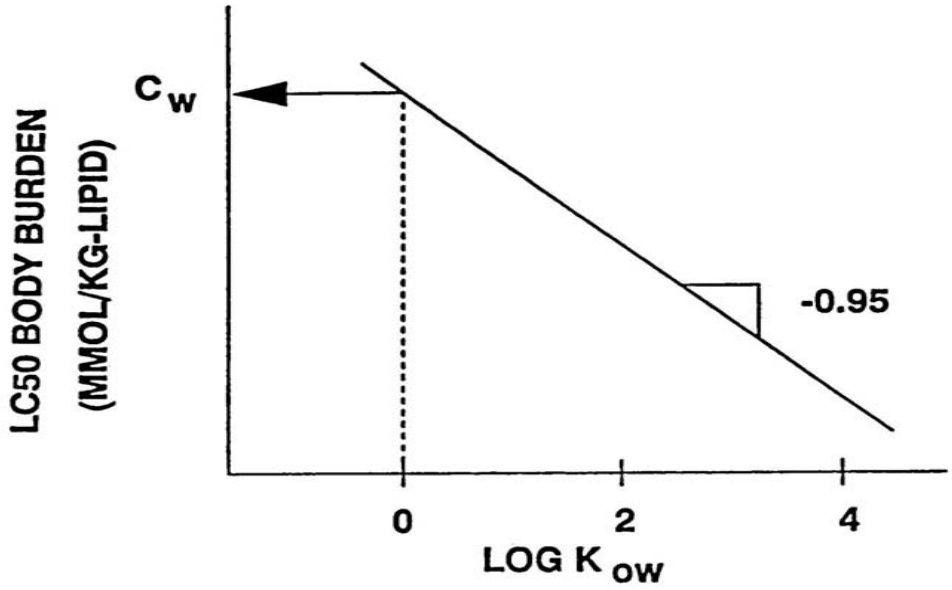
Konemann, H. (1981).. Toxicology, 19, 209-221.



Mackay, D. Environ. Sci. Technol. 1982, 16, 274

McCarty, L. S., D. Mackay, A.D. Smith, G.W. Ozburn, & Dixon, D. G. (1991).
Interpreting aquatic toxicity QSARs: the significance of toxicant body residues at the pharmacologic endpoint.
In QSAR In Environmental Toxicology. IV. Amsterdam: Elsevier.

Interpretation of Y-Intercept



$K_{OW} = 1$

$C_{OCTANOL} = C_w$

ASSUME: OCTANOL ~ LIPID

$C_{LIPID} = C_w$

$\therefore$ C_w = LC50 BODY BURDEN (MMOL/KG-LIPID)

Target Lipid Model

CBB = BCF × LC50

$$\log(LC50) = \log(C_L^*) - \log(K_{LW})$$

Linear free energy relationship (LFER)

$$\log(K_{LW}) = a_0 + a_1 \log(K_{OW})$$

Therefore

$$\log(LC50) = \underbrace{\log(C_L^*)}_{\text{Biological}} \quad \underbrace{-a_0 - a_1 \log(K_{OW})}_{\text{Chemical}}$$

Target lipid Model

Slope is same for all organisms

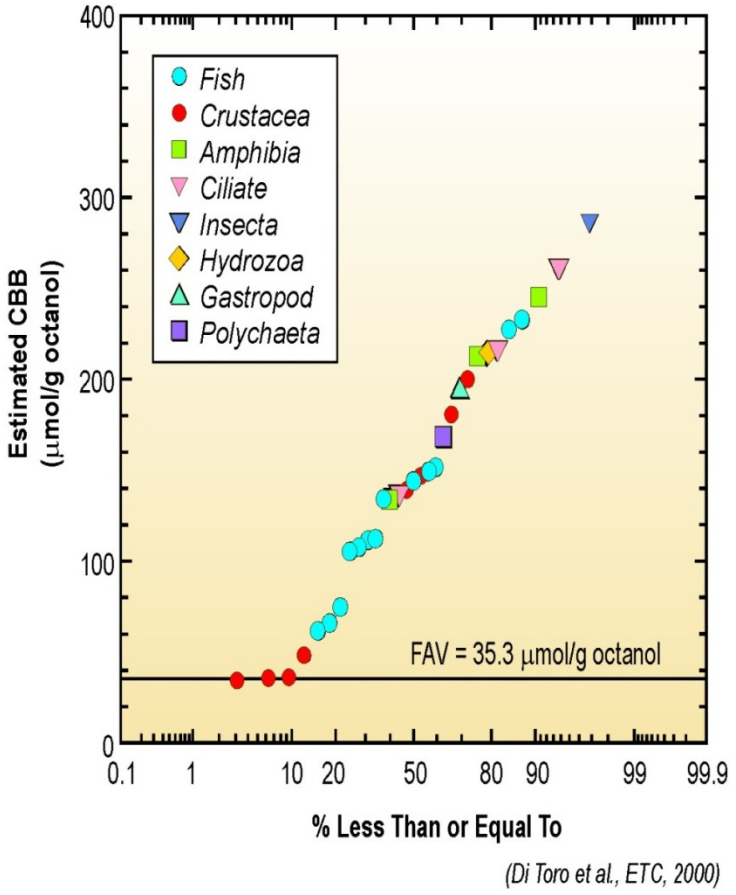
Intercept is Organism specific

$\text{Log } K_{LW} = m \text{ Log } K_{OW}$ + Chemical Class Corrections
(Halogenated, Ketones, PAHs)

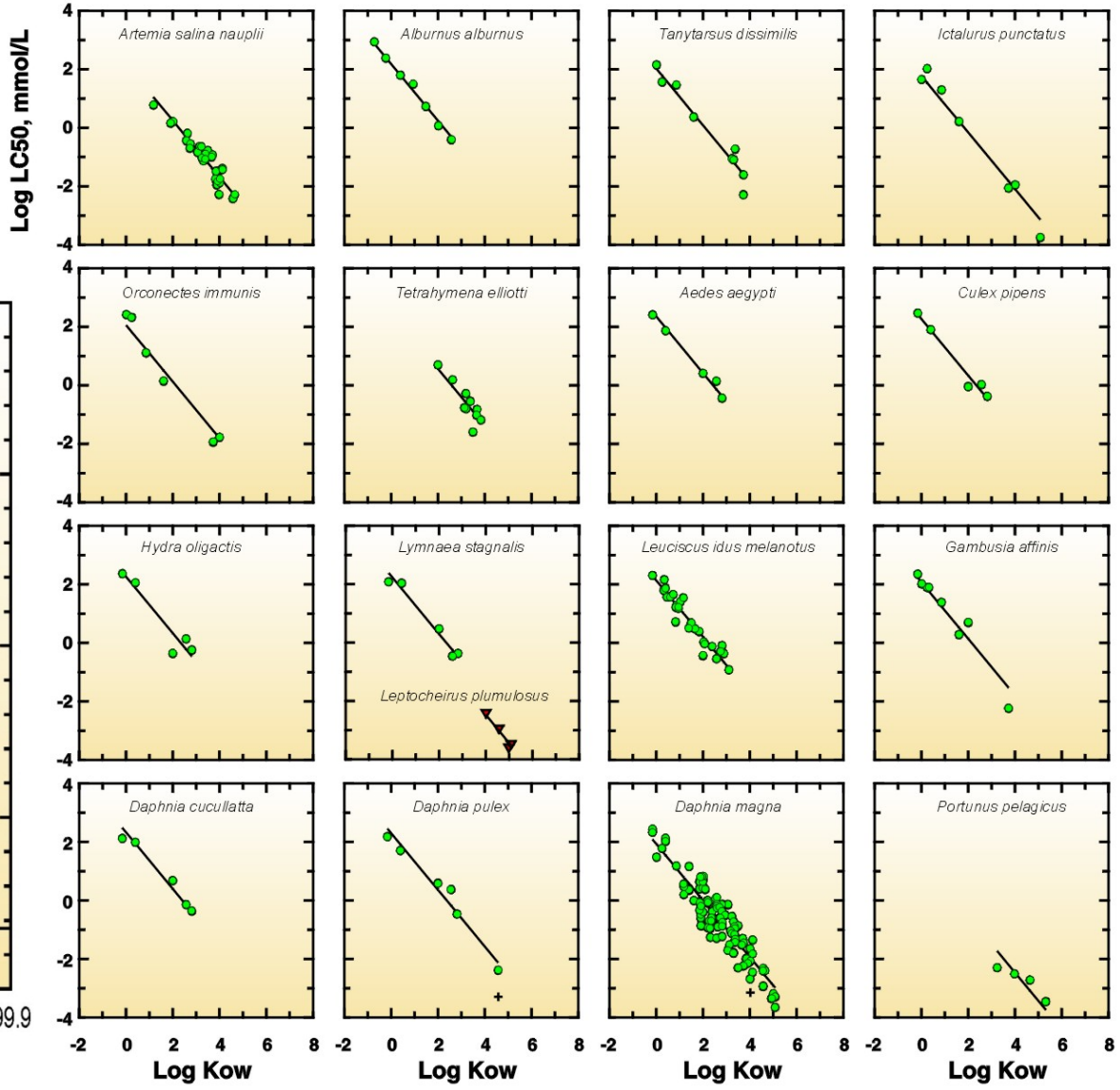
Di Toro DM, McGrath JA, Hansen DJ. 2000. Technical basis for narcotic chemicals and polycyclic aromatic hydrocarbon criteria. I. Water and tissue. Environ Toxicol Chem 19: 1951-1970

Di Toro DM, McGrath JA. 2000. Technical basis for narcotic chemicals and polycyclic aromatic hydrocarbon criteria. II. Mixtures and sediments. Environ Toxicol Chem 19: 1971-1982.

Target Lipid Model

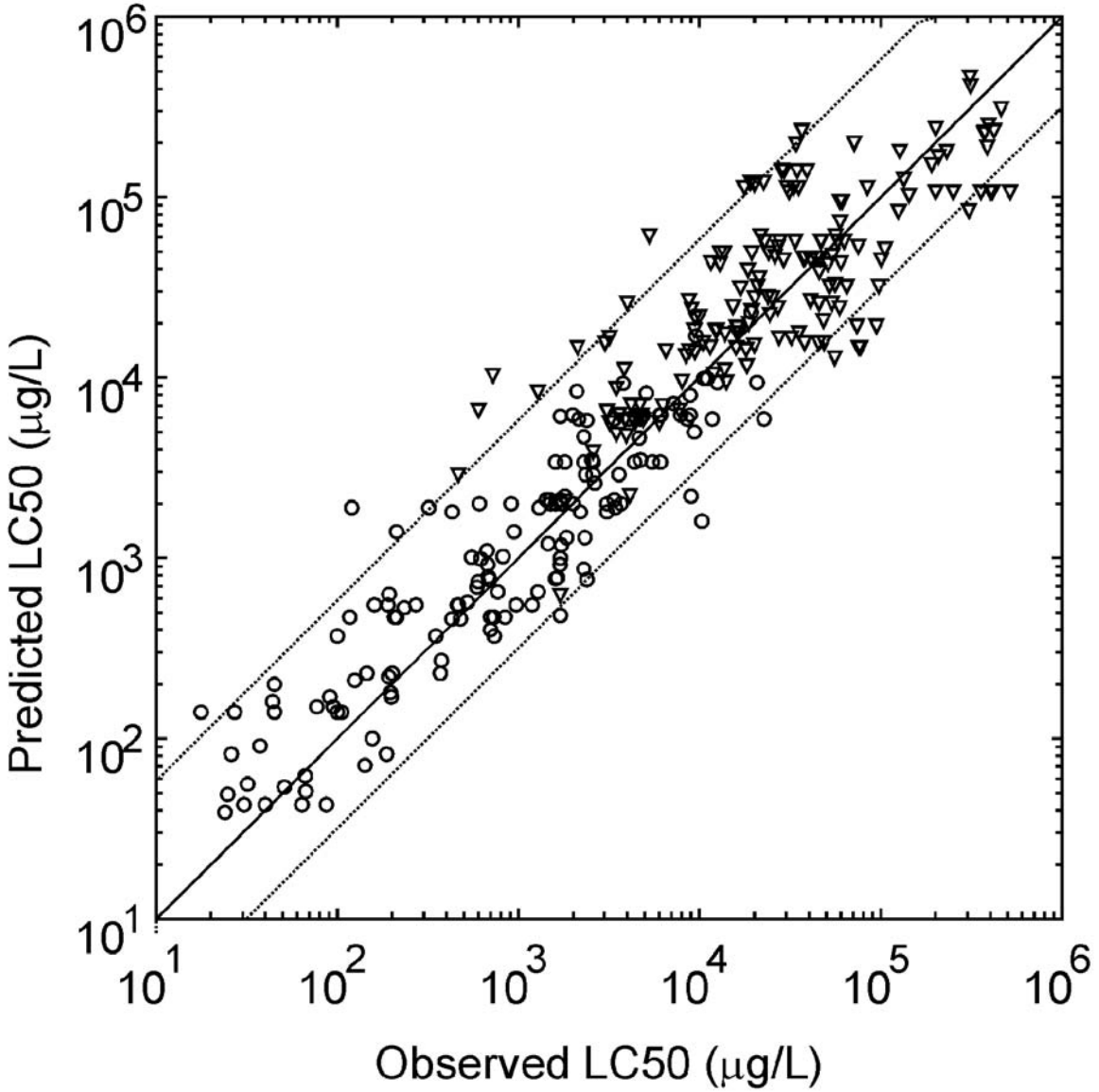


(Di Toro et al., ETC, 2000)



(Di Toro et al., ETC, 2000)

Predicted vs Observed PAH Toxicity



Toxicity of Mixtures

Toxic Units (TU)

$$\text{TU} = \frac{\text{Concentration}}{\text{LC50}}$$

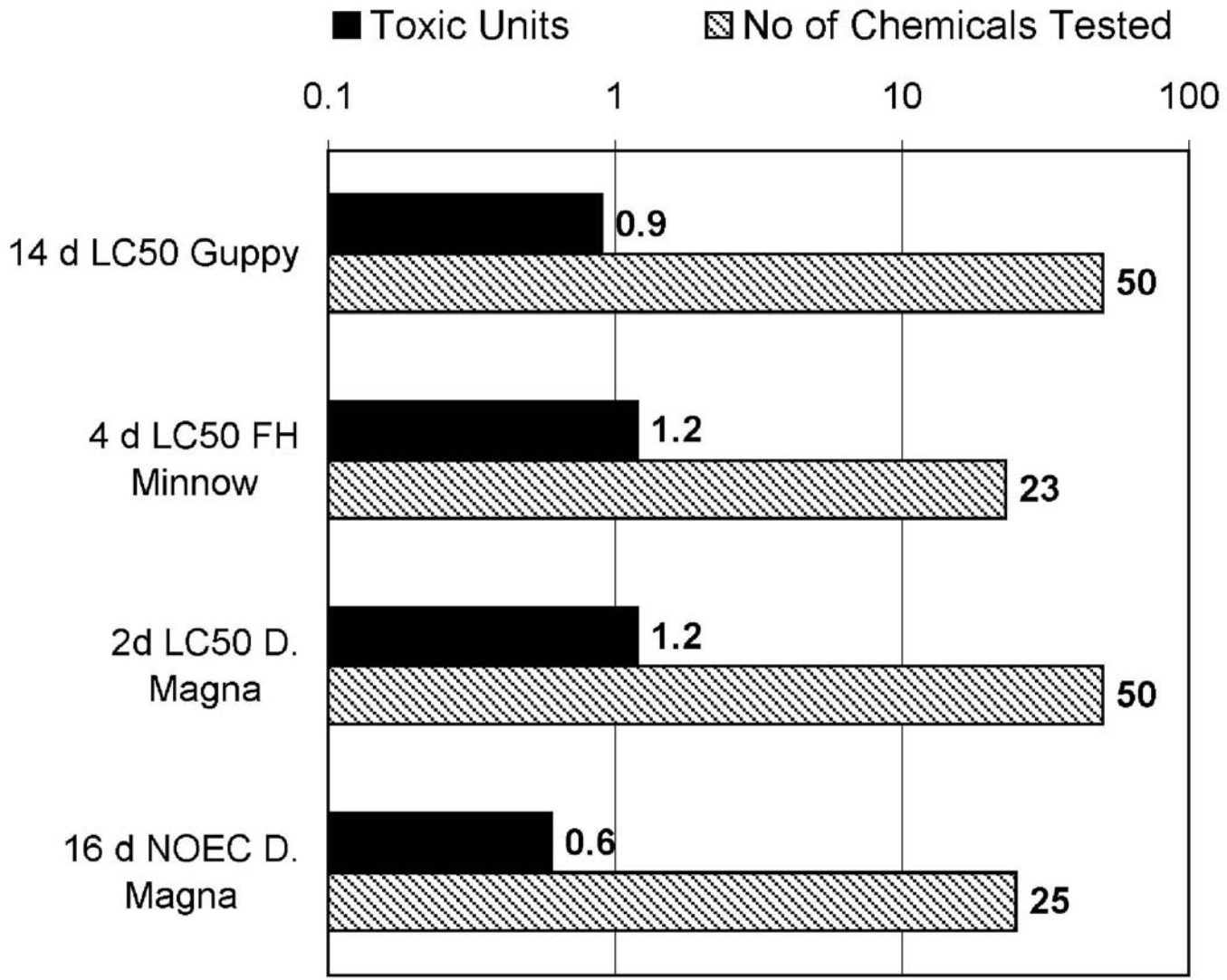
Additivity

$$\text{TU}_{\text{Mixture}} = \sum_i \text{TU}_i$$

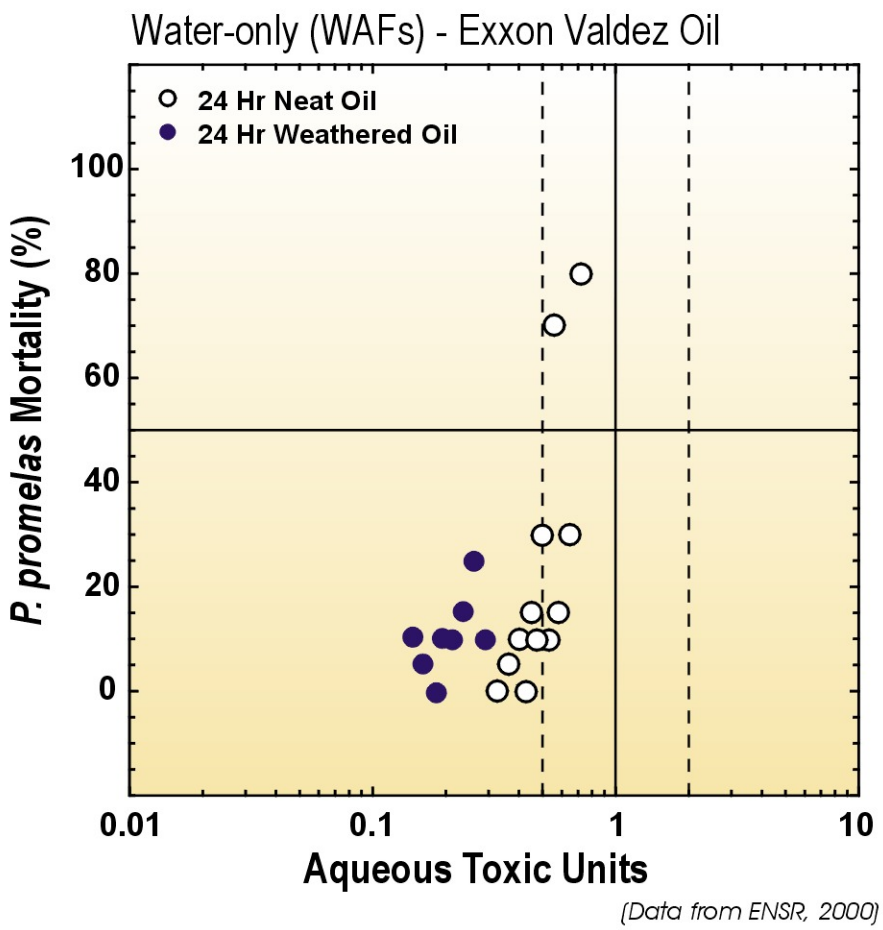
Example

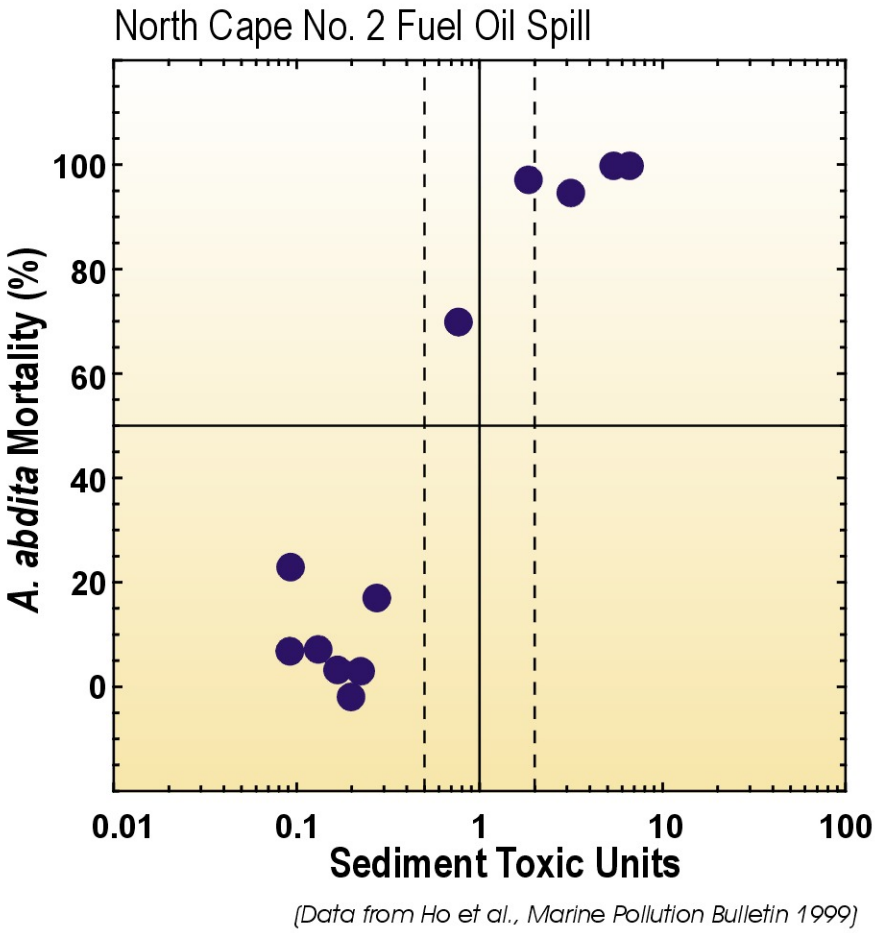
Chemical	Concentration (μg/L)	LC50	TU
Naphthalene	100.0	328.0	0.31
Pyrene	2.5	3.45	0.72
Mixture			1.03

Narcosis Additivity



Target Lipid Model
PAH Mixtures

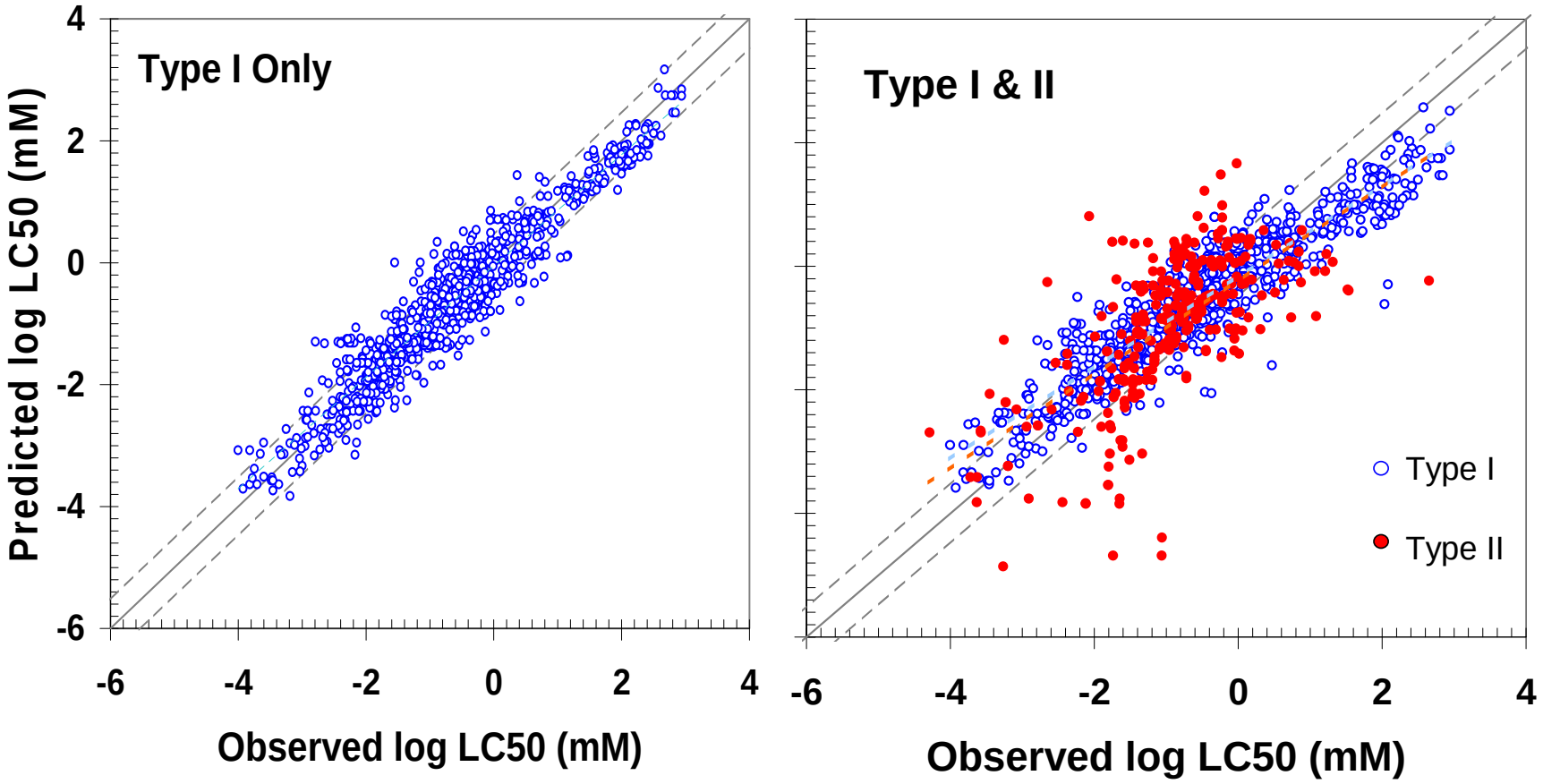




McGrath JA, Di Toro DM. 2009. Validation of the target lipid model for toxicity assessment of residual petroleum constituents: monocyclic and polycyclic aromatic hydrocarbons. Environl Toxicol and Chem 28(6): 1130-1148

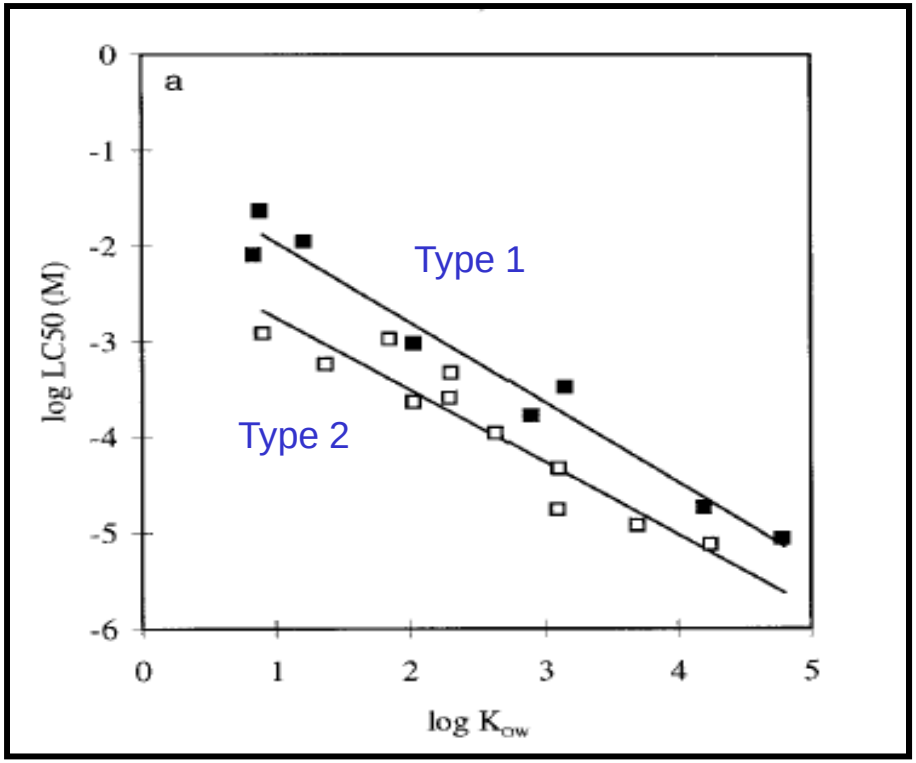
Nonpolar and Polar Chemical Toxicity
- Octanol -

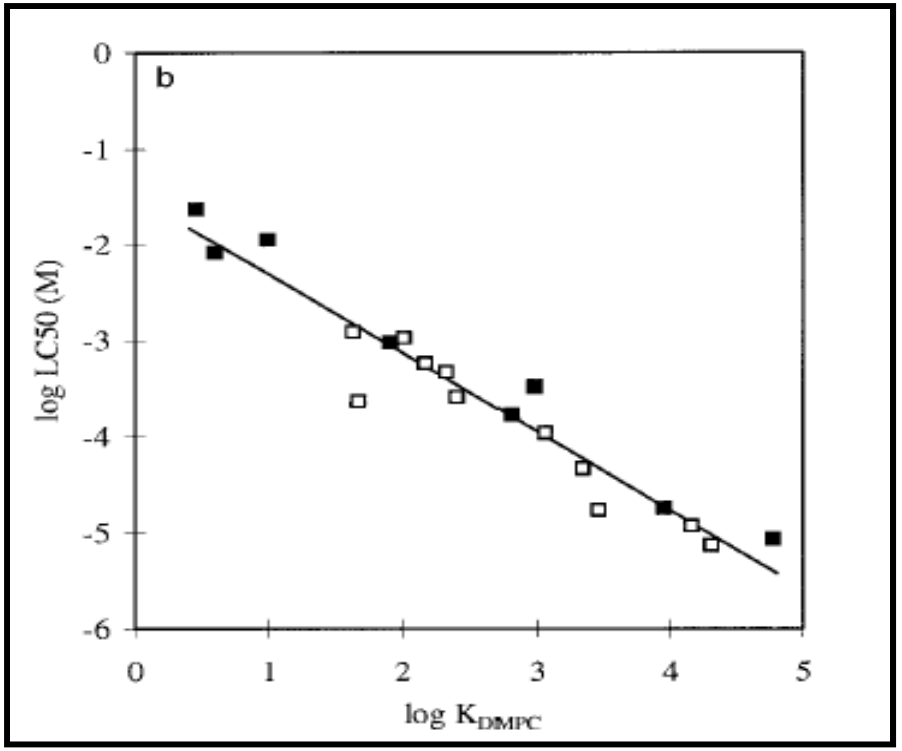
Type II Compounds: Phenols, Amino, Anilines, Nitro, Nitriles, N-heterocycles,

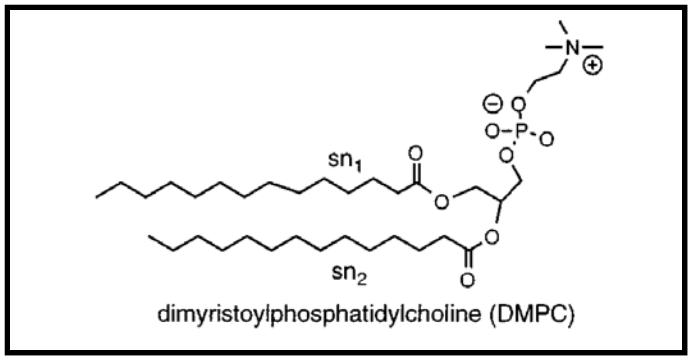


Di Toro, D.M., J.A. McGrath, and D.J. Hansen, Technical basis for narcotic chemicals and polycyclic aromatic hydrocarbon criteria. I. Water and tissue. Environ.Toxicol.Chem., 2000. 19: p. 1951-1970.

DMPC as Target Lipid
LC50 vs K_{OW} and K_{DMPC}







Vaes,HJ, Ramos,EU Verhaar,HJM Hermens,JLM 1997. Acute toxicity of nonpolar versus polar narcosis: Is there a difference? ETC 17:7 pp1380-1384

The Age of Linear Solvation Energy Relationships (LSER/LFER)

$$\text{Log } K_{OC} = c + eE + sS + aA + bB + vV$$

Solvent * Solute
(lower case) * (upper case)

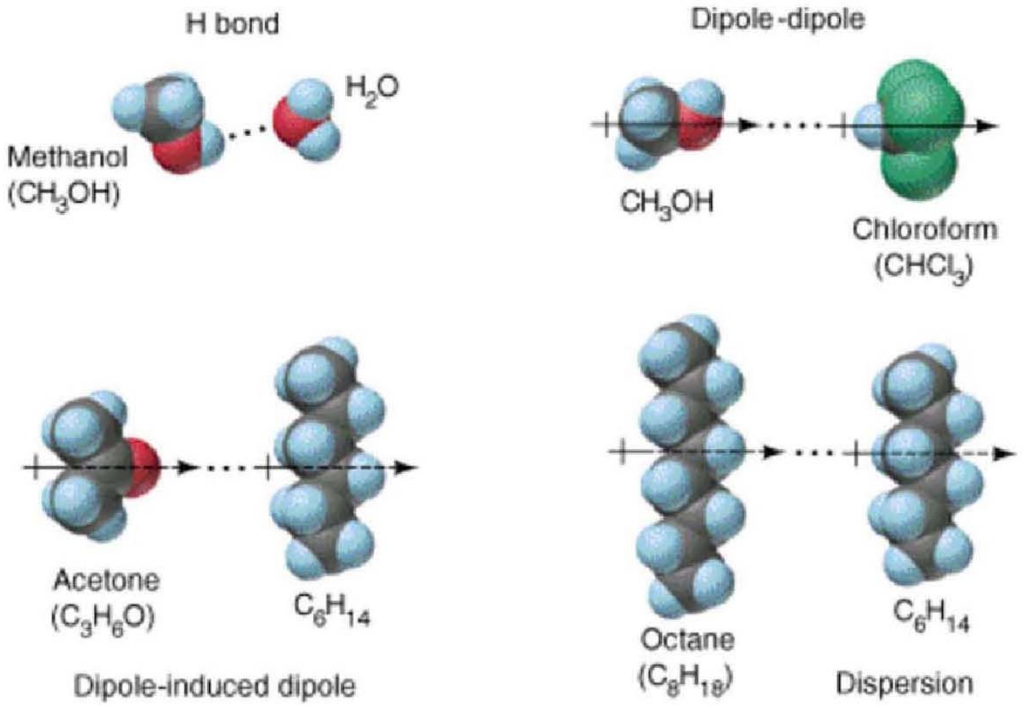
eE – excess molar refractivity

sS – (di)polarizability

aA – hydrogen-bond acidity

bB – hydrogen-bond basicity

vV – molar volume



http://www.science.uwaterloo.ca/~cchieh/cact/c123/intermol.html

Abraham MH, Chadha HS, Whiting GS, Mitchell RC Hydrogen Bonding 32 An analysis of water-octanol and water-alkane partition J. Pharmaceutical Sciences 83(8) 1994

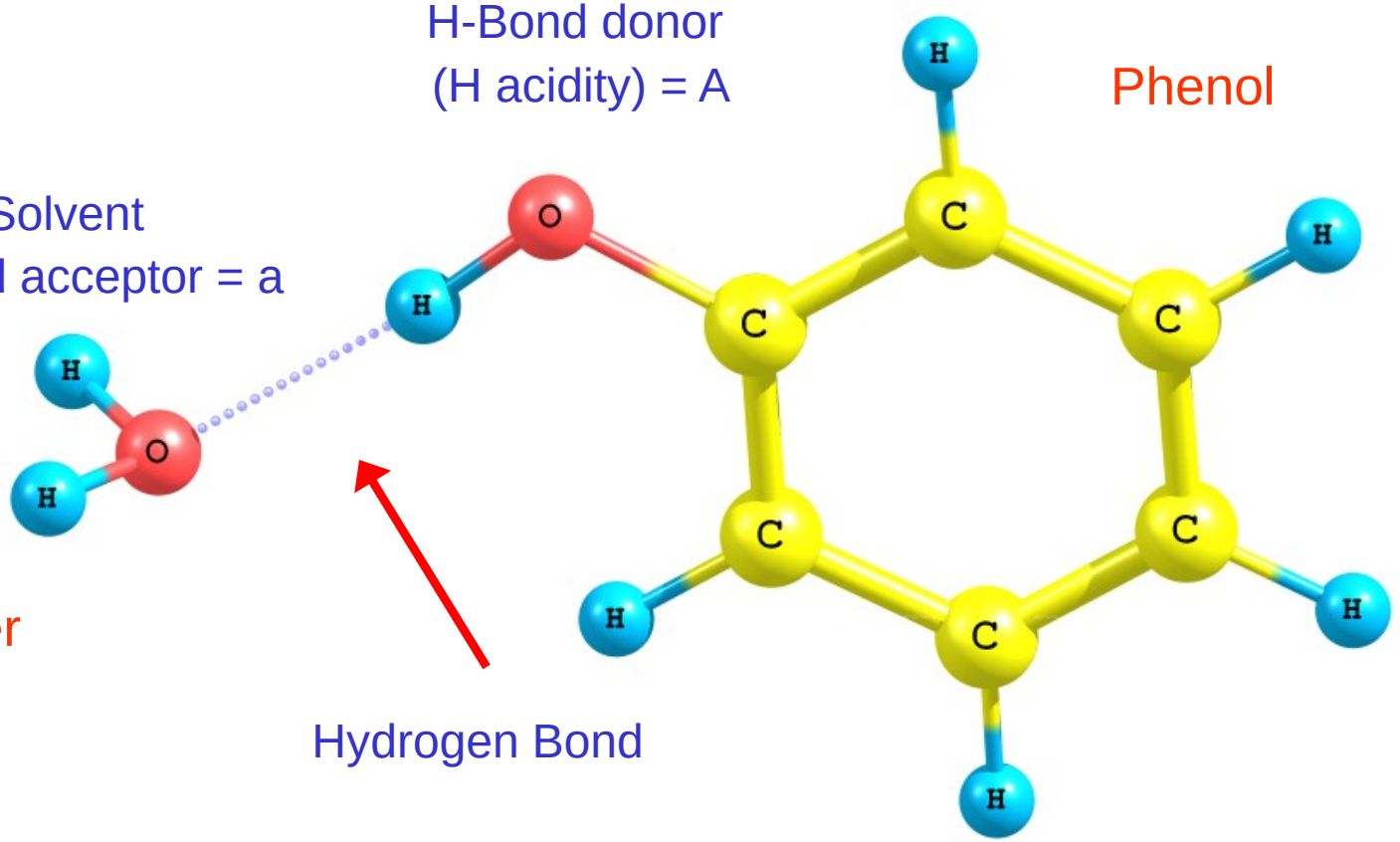
Goss, K., & Schwarzenbach, R. P. (2001). Linear Free Energy Relationships Used To Evaluate Equilibrium Partitioning of Organic Compounds. Environ. Sci. Technol., 35(1), 1-9.

Hydrogen Bonding – Donor

Solute
H-Bond donor
(H acidity) = A

Phenol

Solvent
H-Bond acceptor = a



Water

Hydrogen Bond

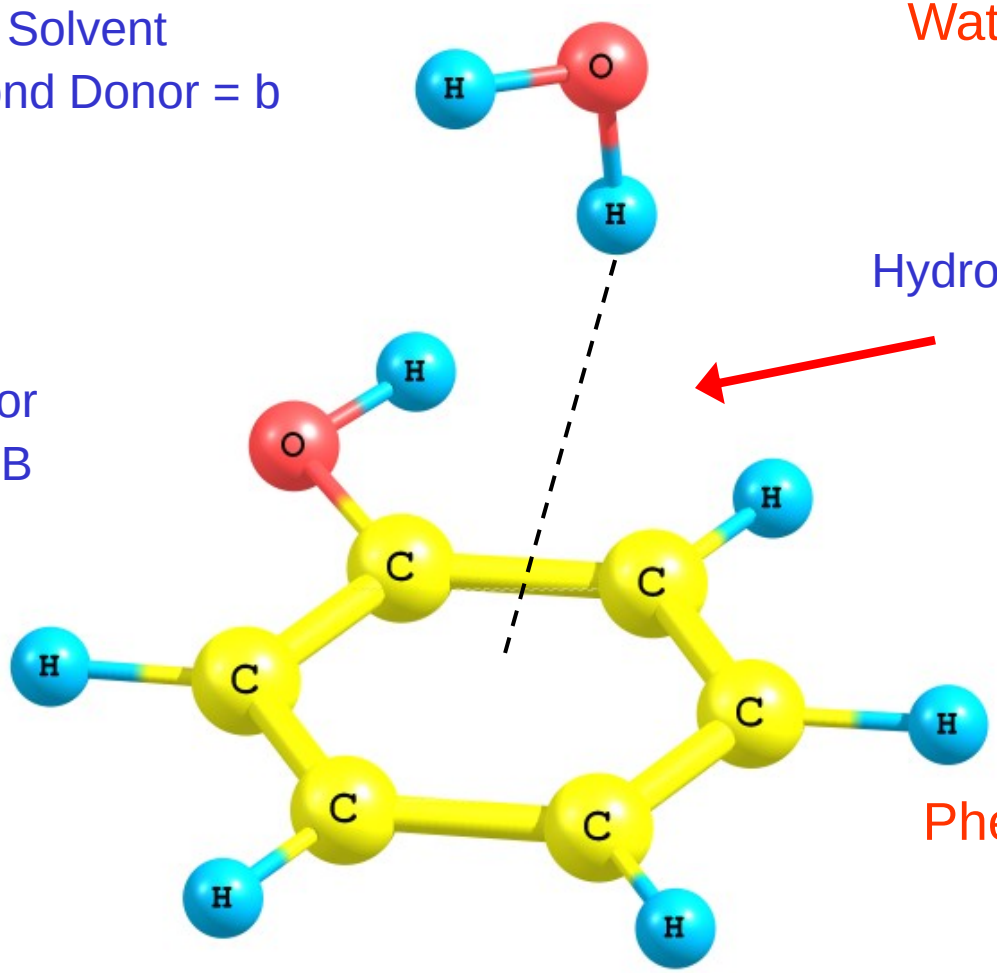
Hydrogen Bonding - Acceptor

Solvent
H-Bond Donor = b

Water

Hydrogen Bond

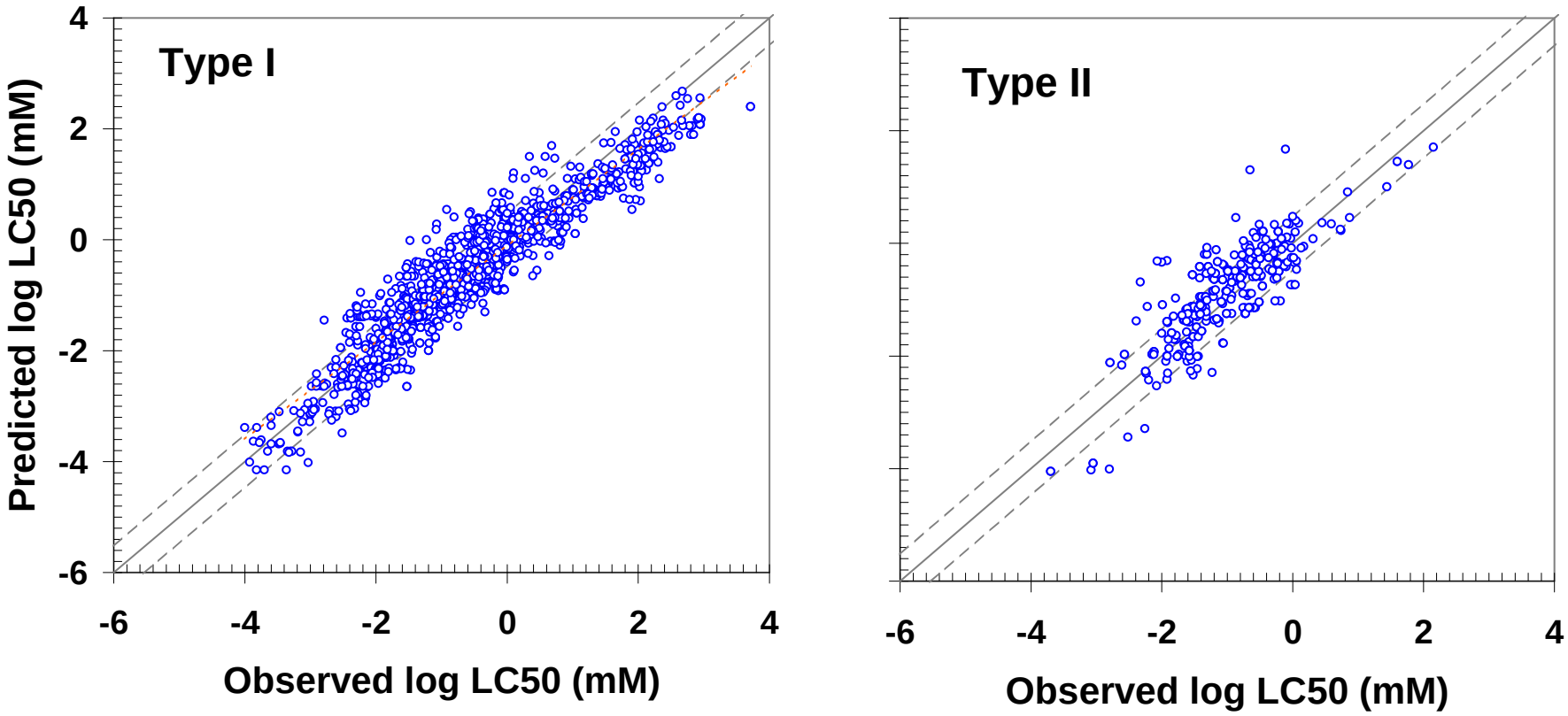
Solute
H-Bond acceptor
(H basicitiy) = B



Phenol

Nonpolar and Polar Chemical Toxicity
- LSER -

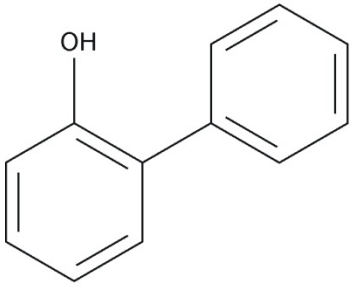
$$K_{LW} = c + eE + sS + aA + bB + vV$$



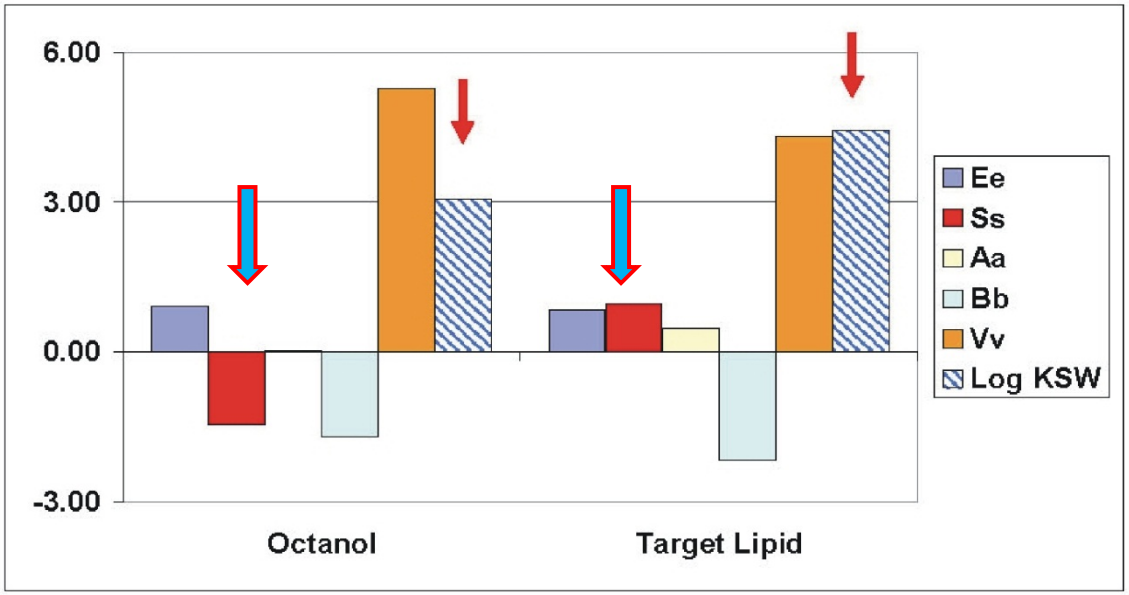
42 species 527 chemicals 1728 data points

Kipka, U. and D.M. Di Toro, Technical basis for polar and nonpolar narcotic chemicals and PAH criteria. III. A polyparameter model for target lipid partitioning. Environmental Toxicology and Chemistry, 2008. 28(7): p. 1429-1438.

2 phenylphenol
Target Lipid & Octanol - Water Partitioning



Solute		Solvents			Partition Coefficient		
2-phenyl phenol			Octanol	Target Lipid		Octanol	Target Lipid
E	1.61	e	0.56	0.52	Ee	0.90	0.84
S	1.37	s	-1.05	0.70	Ss	-1.44	0.96
A	0.50	a	0.03	0.96	Aa	0.02	0.48
B	0.49	b	-3.46	-4.41	Bb	-1.70	-2.16
V	1.38	v	3.81	3.13	Vv	5.27	4.32
					Log K_{SW}	3.06	4.44



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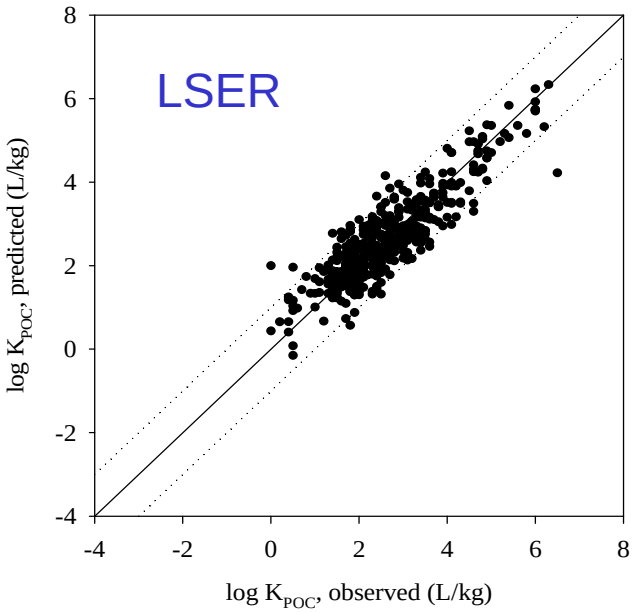
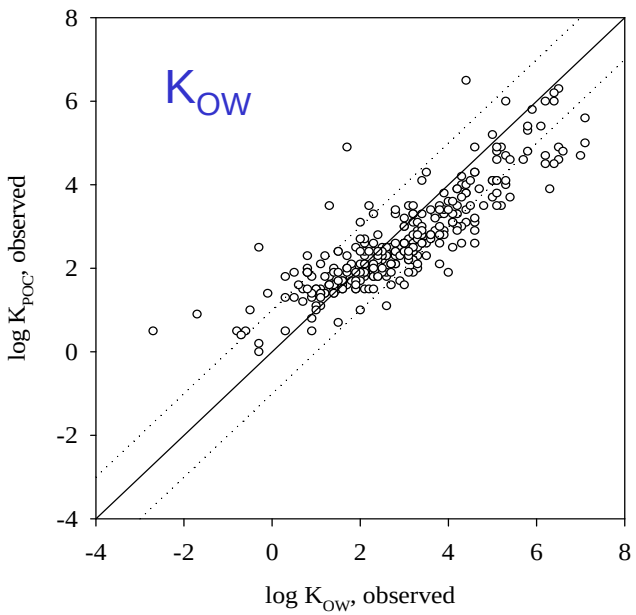
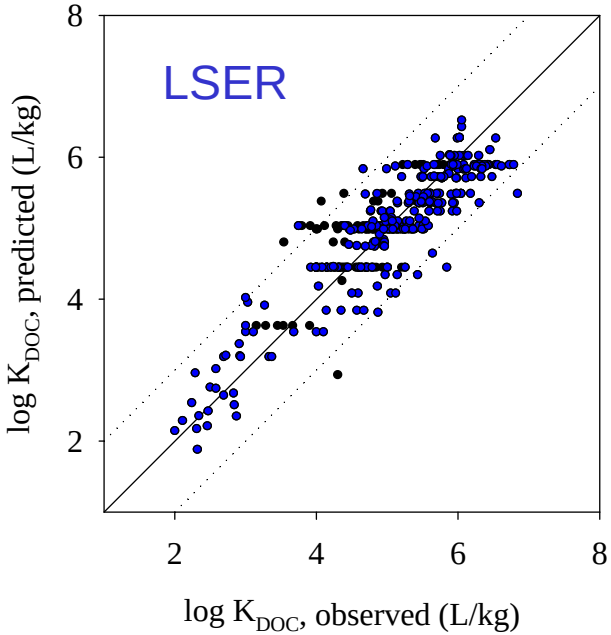
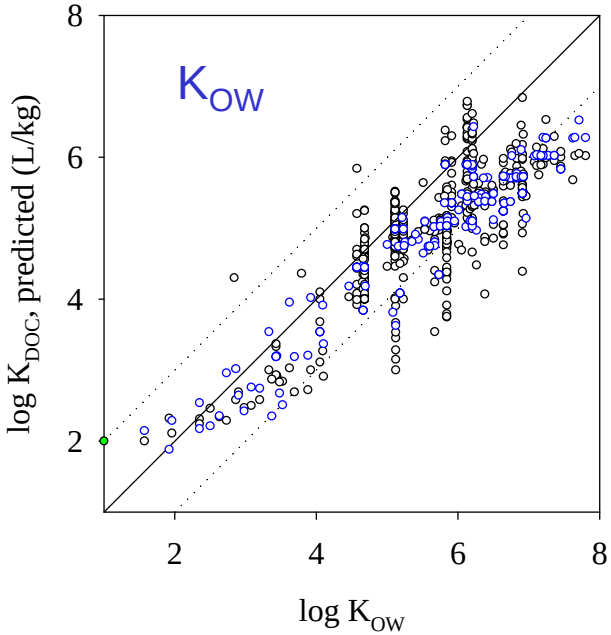
Particulate OC Soils Sediments









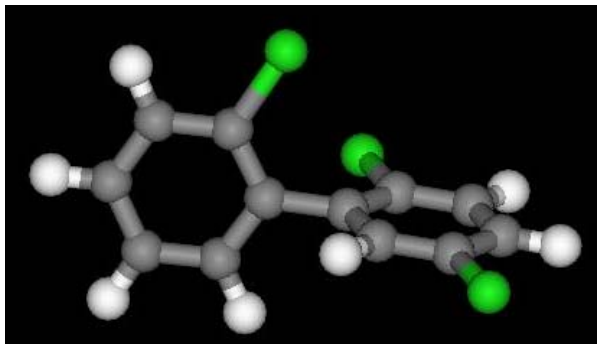
Dissolved OC Humic Acid

Kipka U, Di Toro DM. 2011. A Linear Solvation Energy Relationship Model Of Organic Chemical Partitioning To Particulate Organic Carbon In Soils And Sediments. ETC 30(9): 2013-2022.

The Age of Quantum Chemistry
- COSMO-SAC –
Conductor-like Screening Model – Segment Activity Coefficient

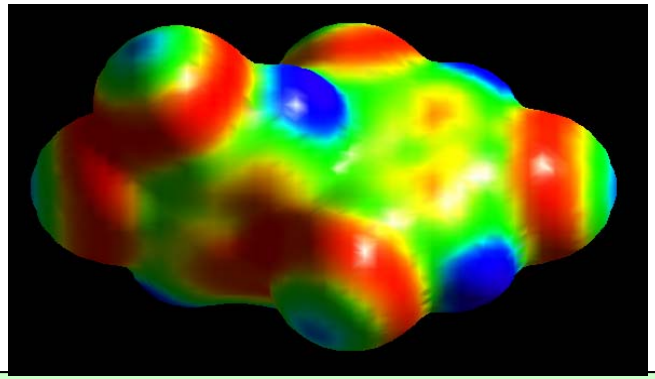
Quantum Mechanics

Gas phase geometry optimization



Liquid phase DFT/ COSMO

Stat. Mechanics

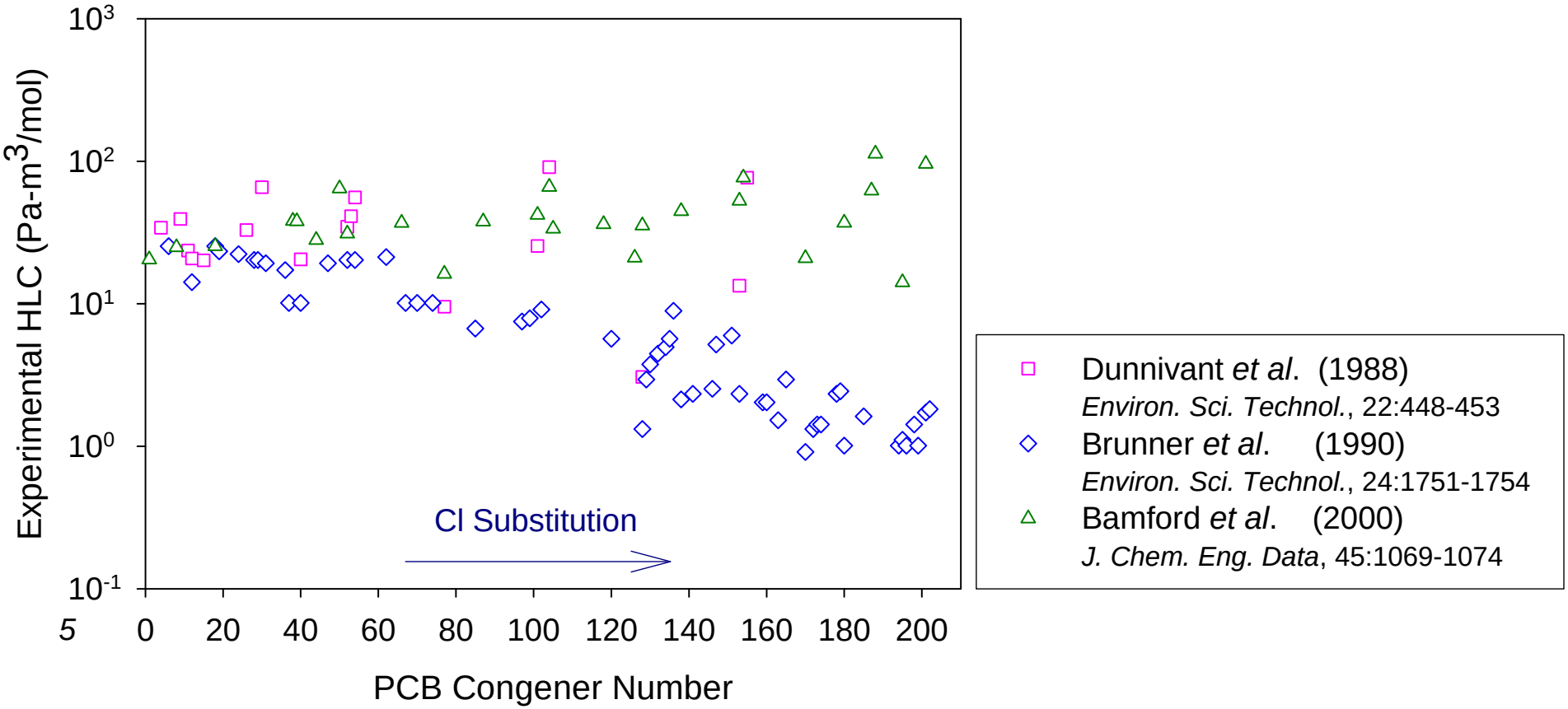


Thermodynamic properties COSMO-SAC

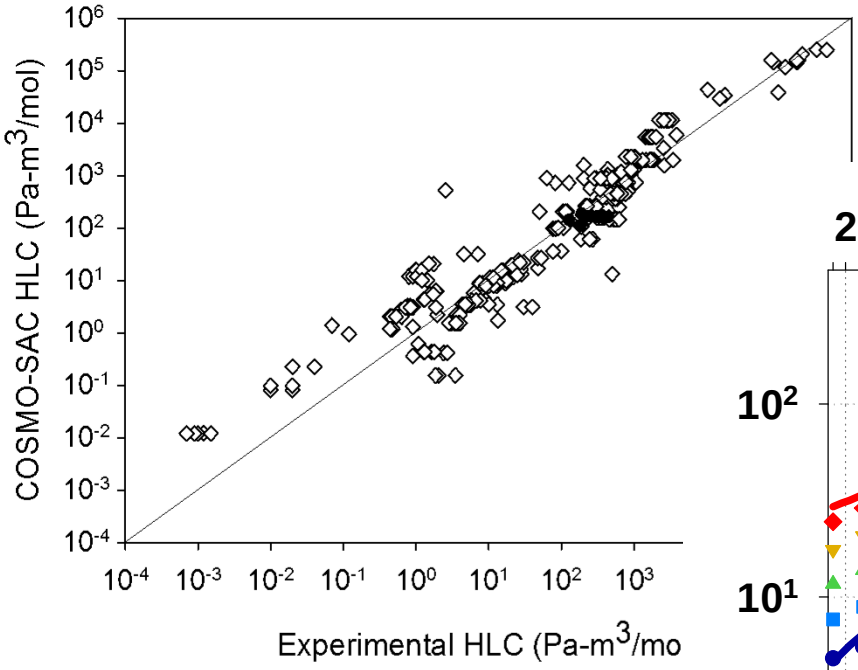
Klamt & Schüürmann (1993) *J. Chem. Soc. Perkin Trans*., 2, 799-805.
Lin & Sandler (2002) *Ind. Eng. Chem. Res*., 41, 899-913.
Lin et al. (2004) *J. Phys. Chem. A,* 108, 7429-7439.

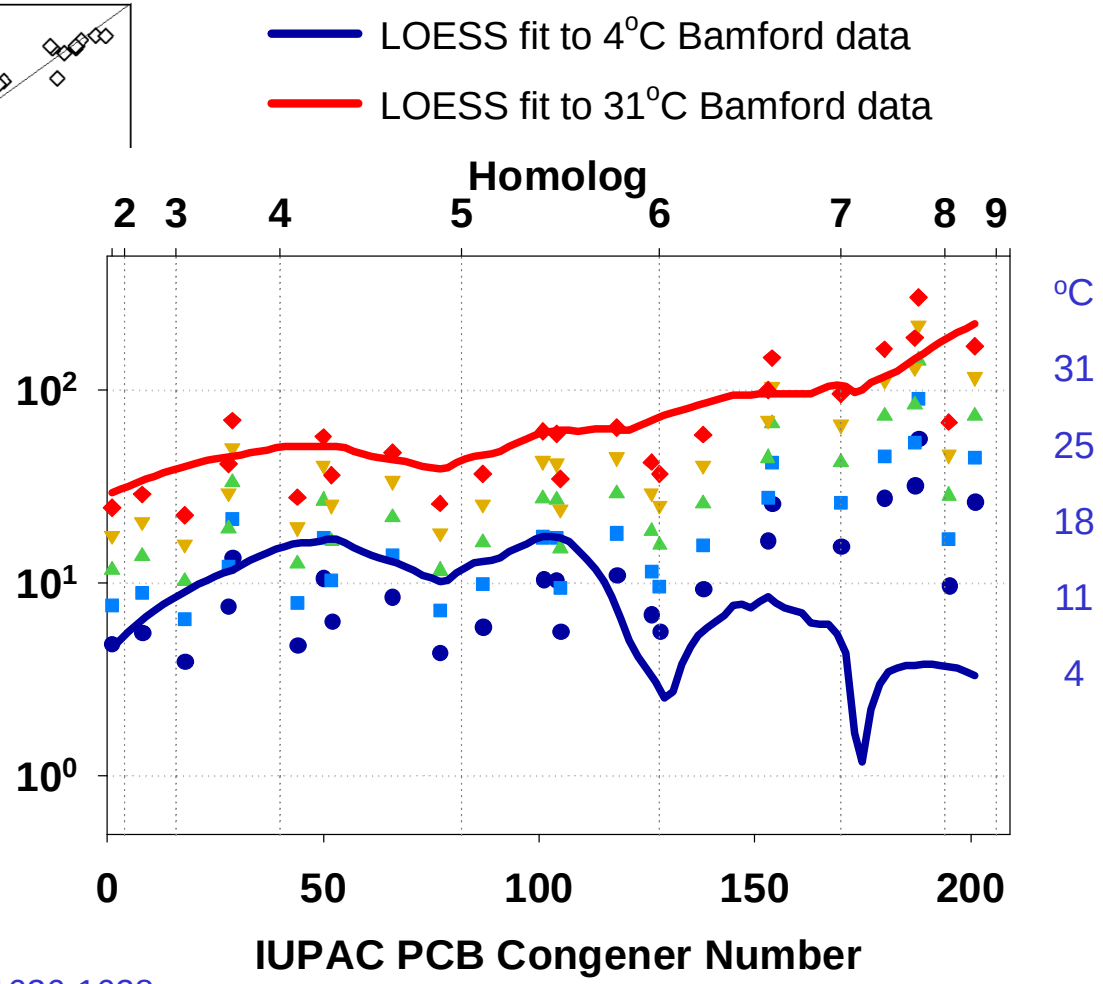
PCBs: Henry's Law Constants

- Henry's law constant (HLC)
  - Equilibrium partitioning between water and air
- Lack of reliable measurements for HLC of PCBs



COSMO-SAC
- Henry's Law Constant -



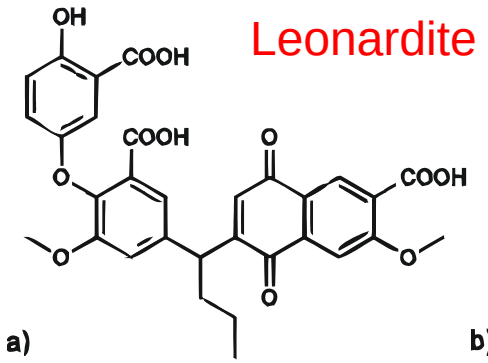


Phillips K. L., Sandler S. I., Greene R. W., and Di Toro D. M. (2008) Environmental Science & Technology 42(22), 8412-8418.

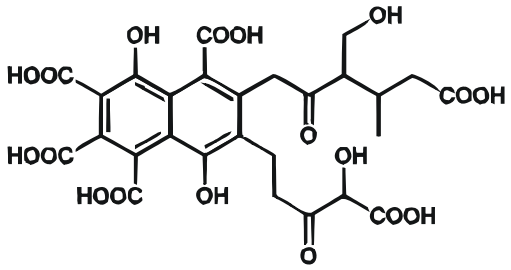
Goss et al. (2004) *Environ. Sci. Technol.*, 38, 1626-1628.
Bamford et al. (2000) *J. Chem. Eng. Data*, 45, 1069-1074.
Bamford et al. (2002) *Environ. Sci. Technol.,* 36, 4395-4402.
Baker et al. (2004) *Environ. Sci. Technol.*, 38, 1629-1632.

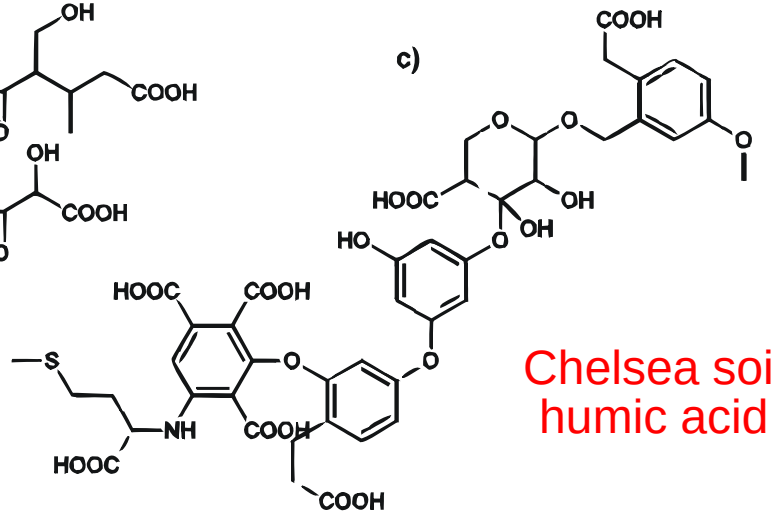
Organic Matter Model Molecules

Leonardite humic acid

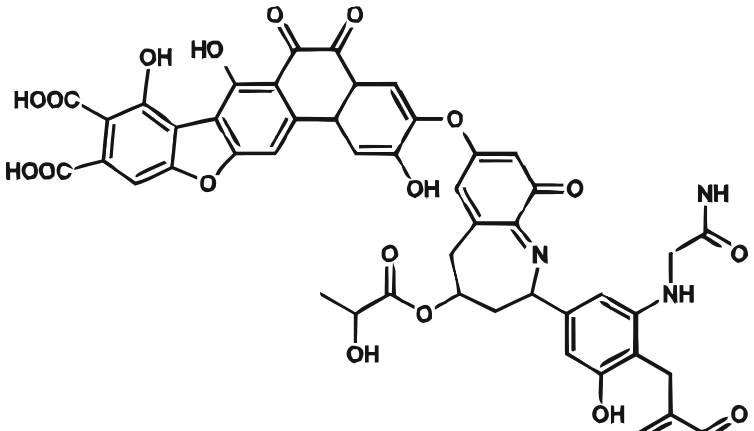


Buffle et al., fulvic acid

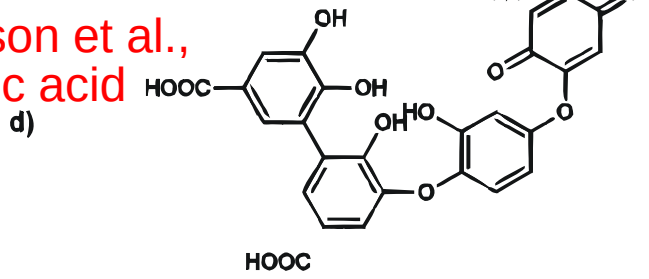




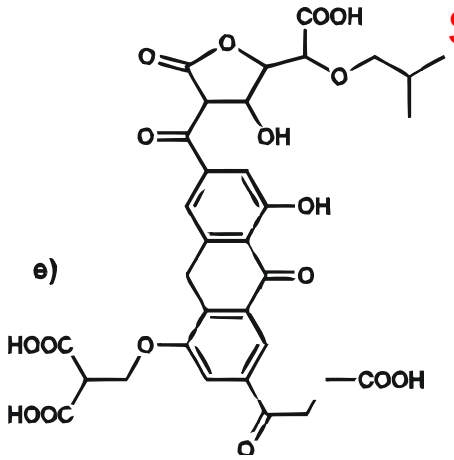
Chelsea soil humic acid



Stevenson et al., humic acid

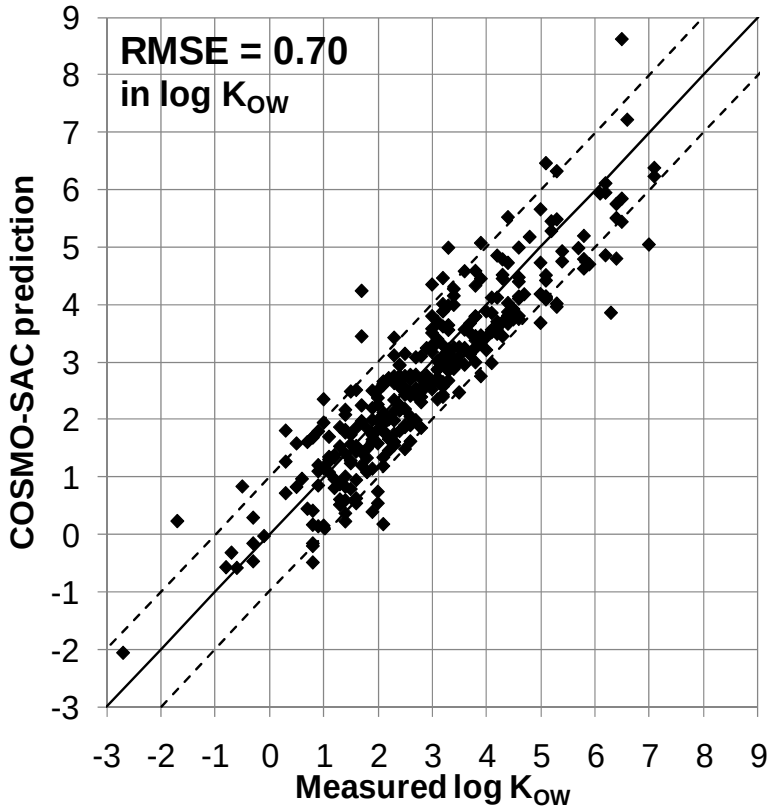


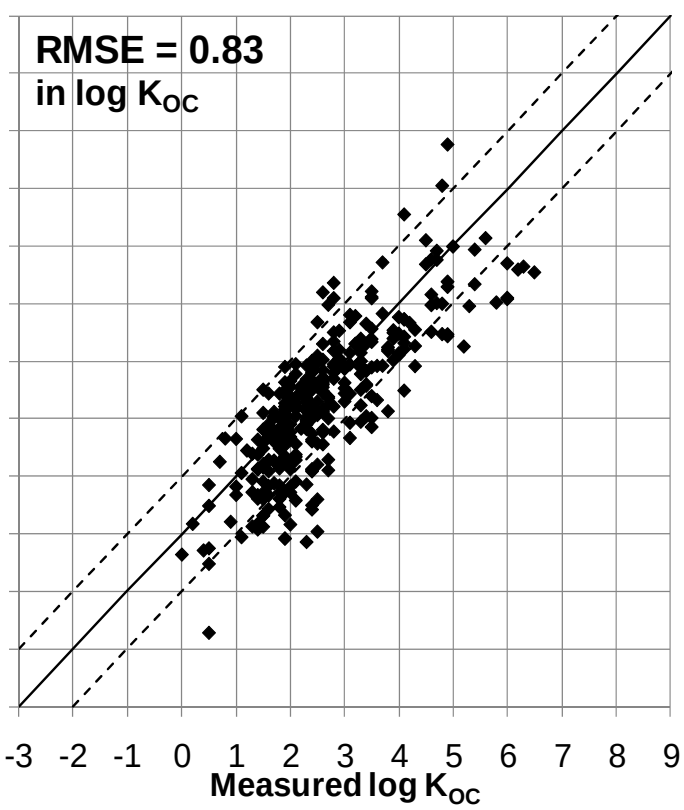
Suwannee river fulvic acid



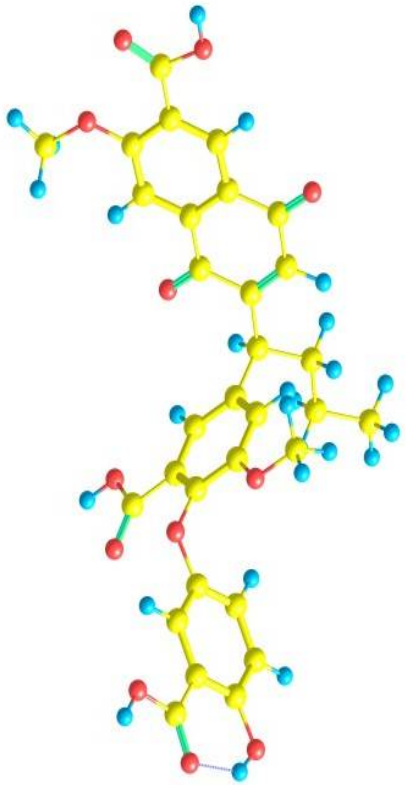
Atalay, Y. B., R. F. Carbonaro, Di Toro DM (2009). "Distribution of Proton Dissociation Constants for Model Humic and Fulvic Acid Molecules." Environmental Science & Technology 43(10): 3626-3631.

COSMO-SAC – Predicted K_{OW} & K_{OC} Humic Acid as Solvent





Leonardite



Phillips KL, Di Toro DM, Sandler SI. 2011. Prediction of Soil Sorption Coefficients using Model Molecular Structures for Organic Matter and the Quantum Mechanical COSMO-SAC Model. Environ Sci & Technol 45(3): 1021-1027

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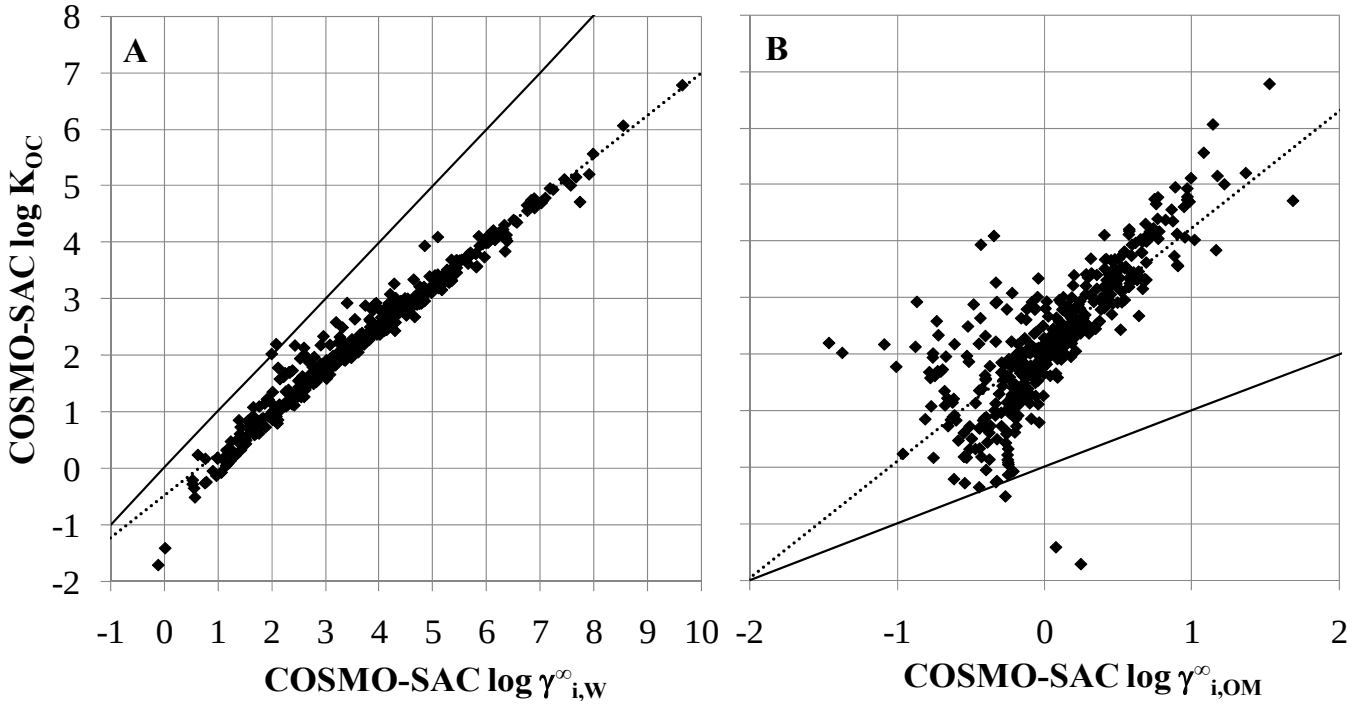
Data: Winget et al. (2000) Environ Sci. Technol. 34, 4733-4740.

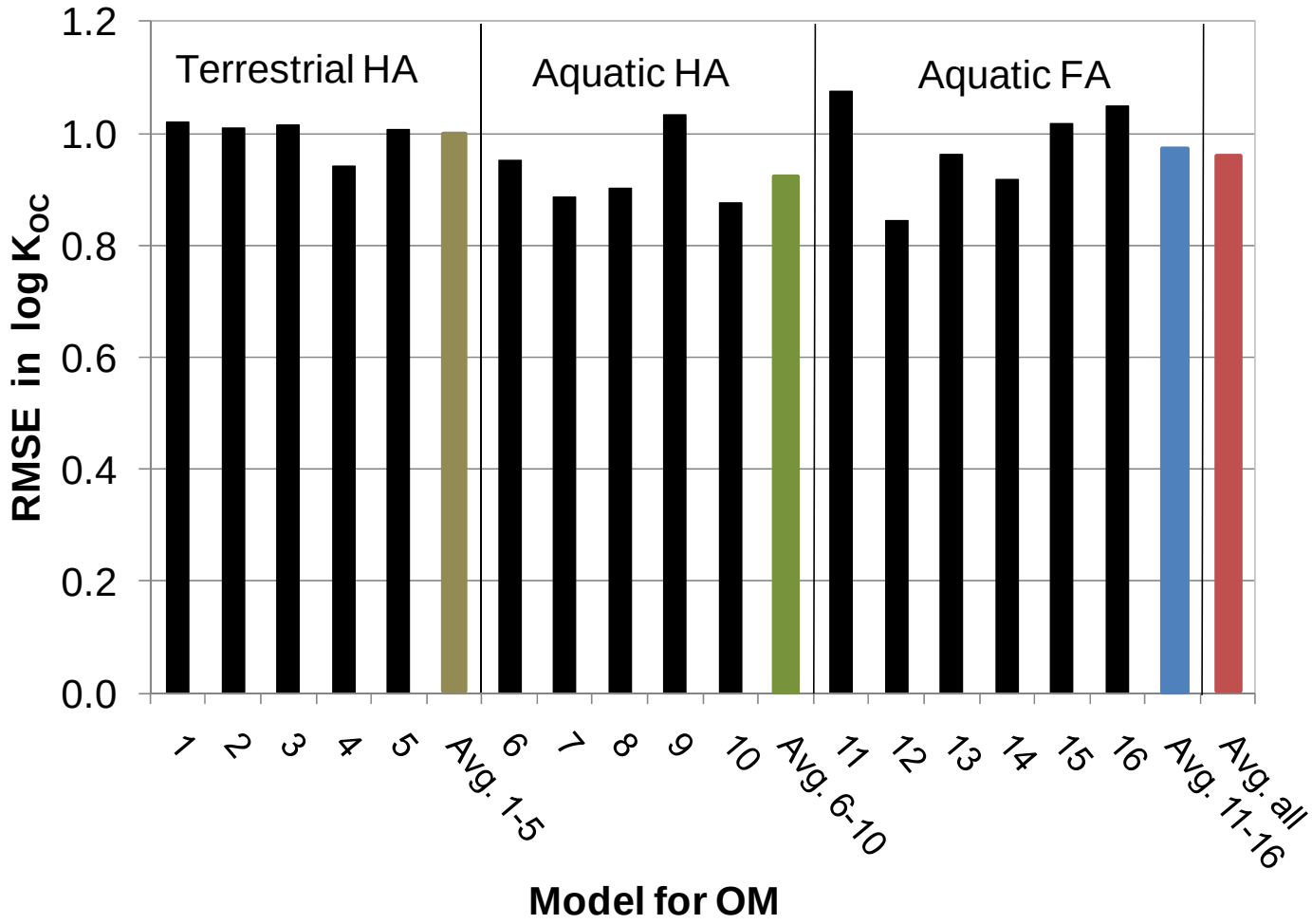
COSMO-SAC
Components of the Prediction

$$K_{OC} = \frac{\gamma^{\infty}_{i,W}}{\gamma^{\infty}_{i,OM}} \frac{MW_W}{MW_{OC}\rho_W n_{C,OM}}$$



Phillips KL, Di Toro DM, Sandler SI. 2011. Prediction of Soil Sorption Coefficients using Model Molecular Structures for Organic Matter and the Quantum Mechanical COSMO-SAC Model. Environ Sci & Technol 45(3): 1021-1027.

COSMO-SAC K_{OC} Prediction Different OM Molecules



Phillips KL, Di Toro DM, Sandler SI. 2011. Prediction of Soil Sorption Coefficients using Model Molecular Structures for Organic Matter and the Quantum Mechanical COSMO-SAC Model. Environ Sci & Technol 45(3): 1021-1027.

Acknowledgements

Students

Yasemin Atalay
Department of Civil and Environmental Engineering
University of Delaware, Newark, Delaware

Undine Kipka
Department of Civil and Environmental Engineering
University of Delaware, Newark, Delaware

Kathy Phillips
Department of Chemical Engineering
University of Delaware, Newark, Delaware

Colleagues

Richard F. Carbonaro
Department of Civil and Environmental Engineering
Manhattan College. Riverdale, NY

Stanley I. Sandler
Department of Chemical Engineering
University of Delaware, Newark, Delaware

Joy McGrath
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