Quantitative Structure-Permeability Relationships – Useful or Useless?

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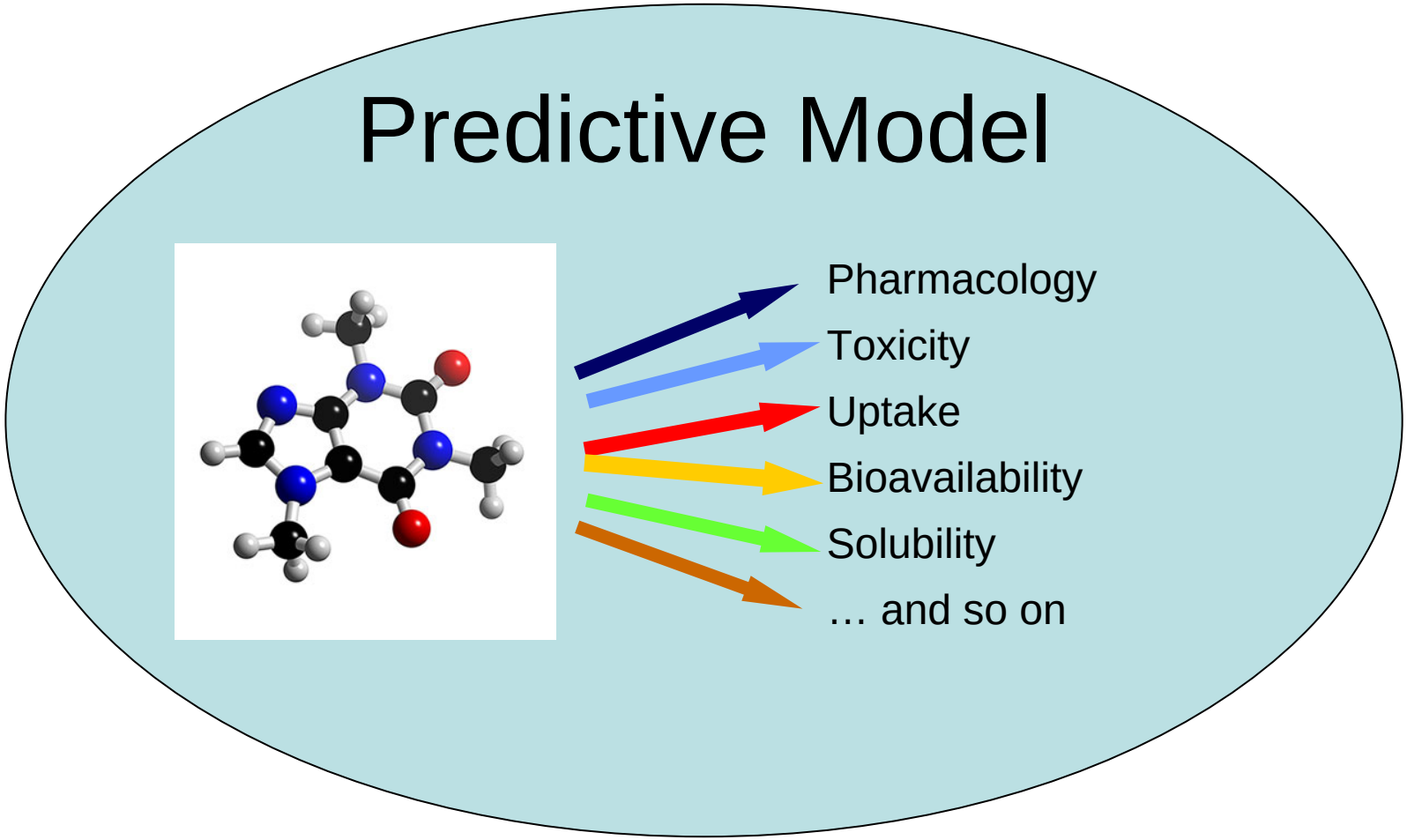
In Silico Predictions in Biology and Chemistry



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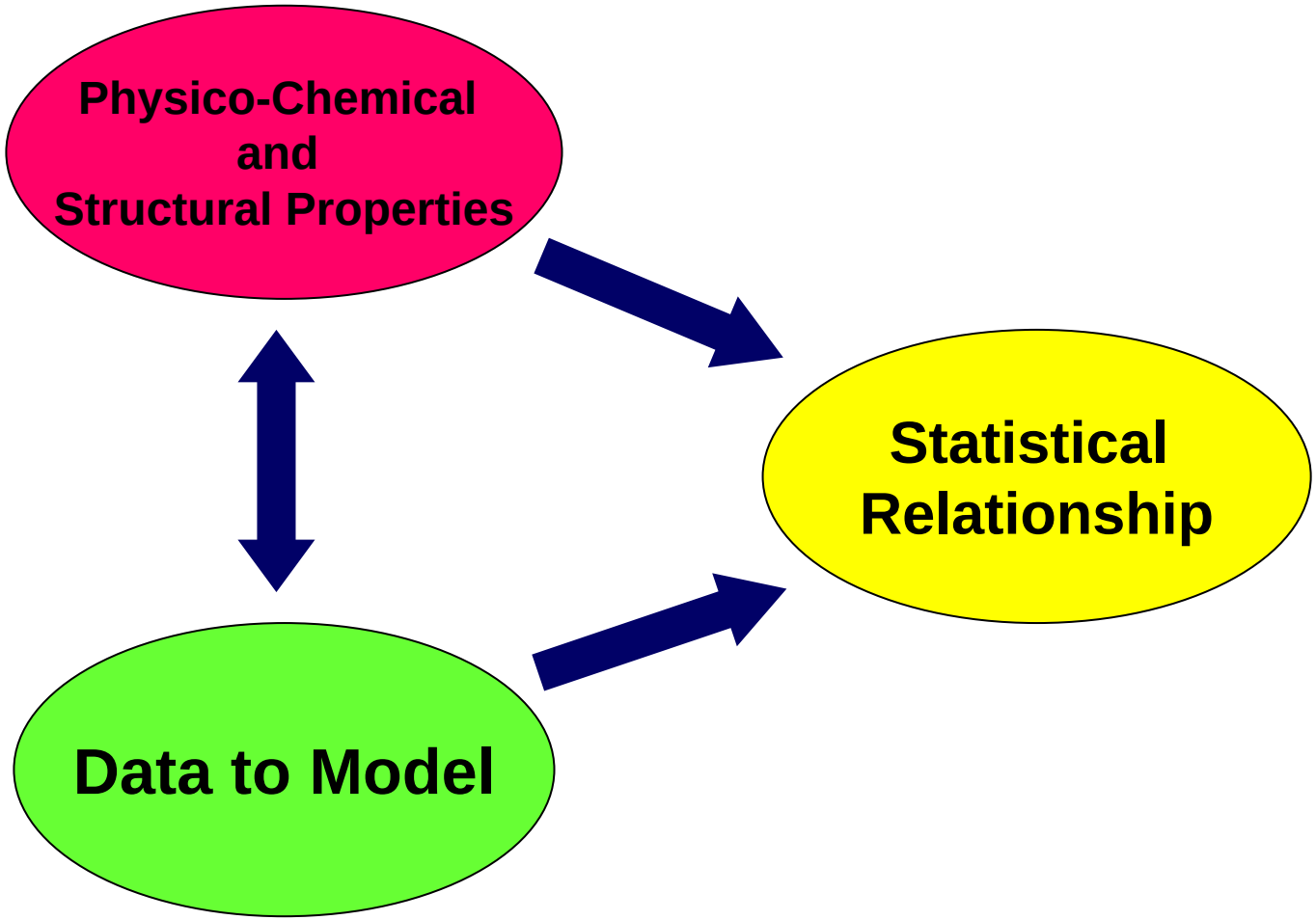

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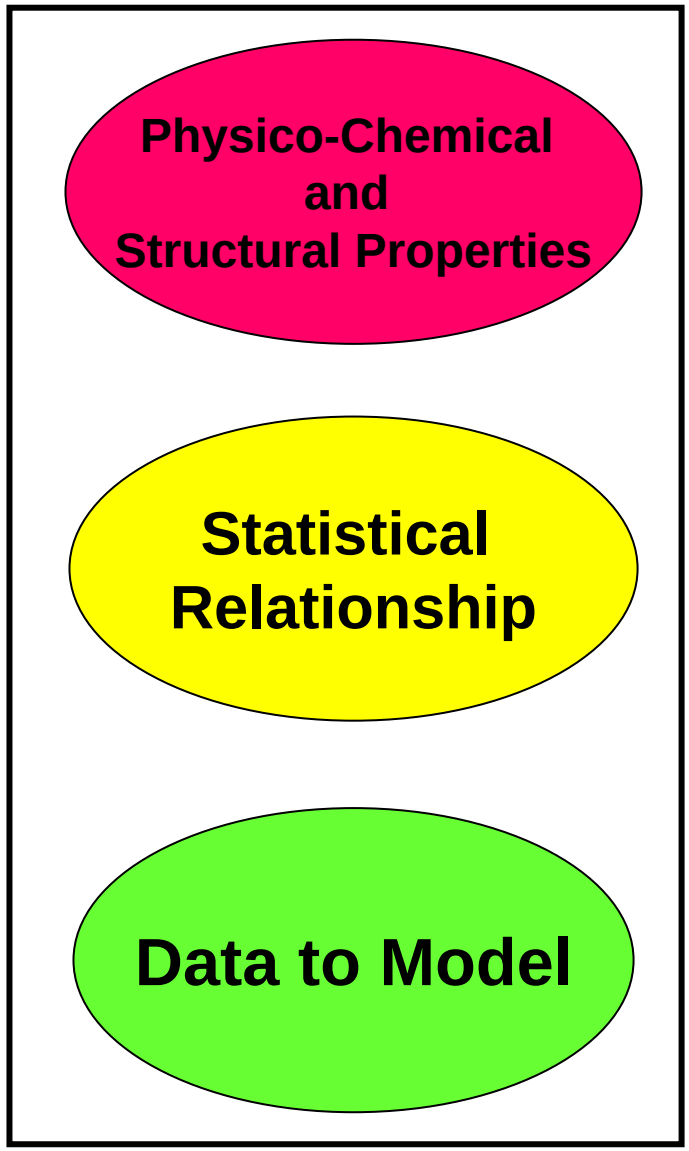

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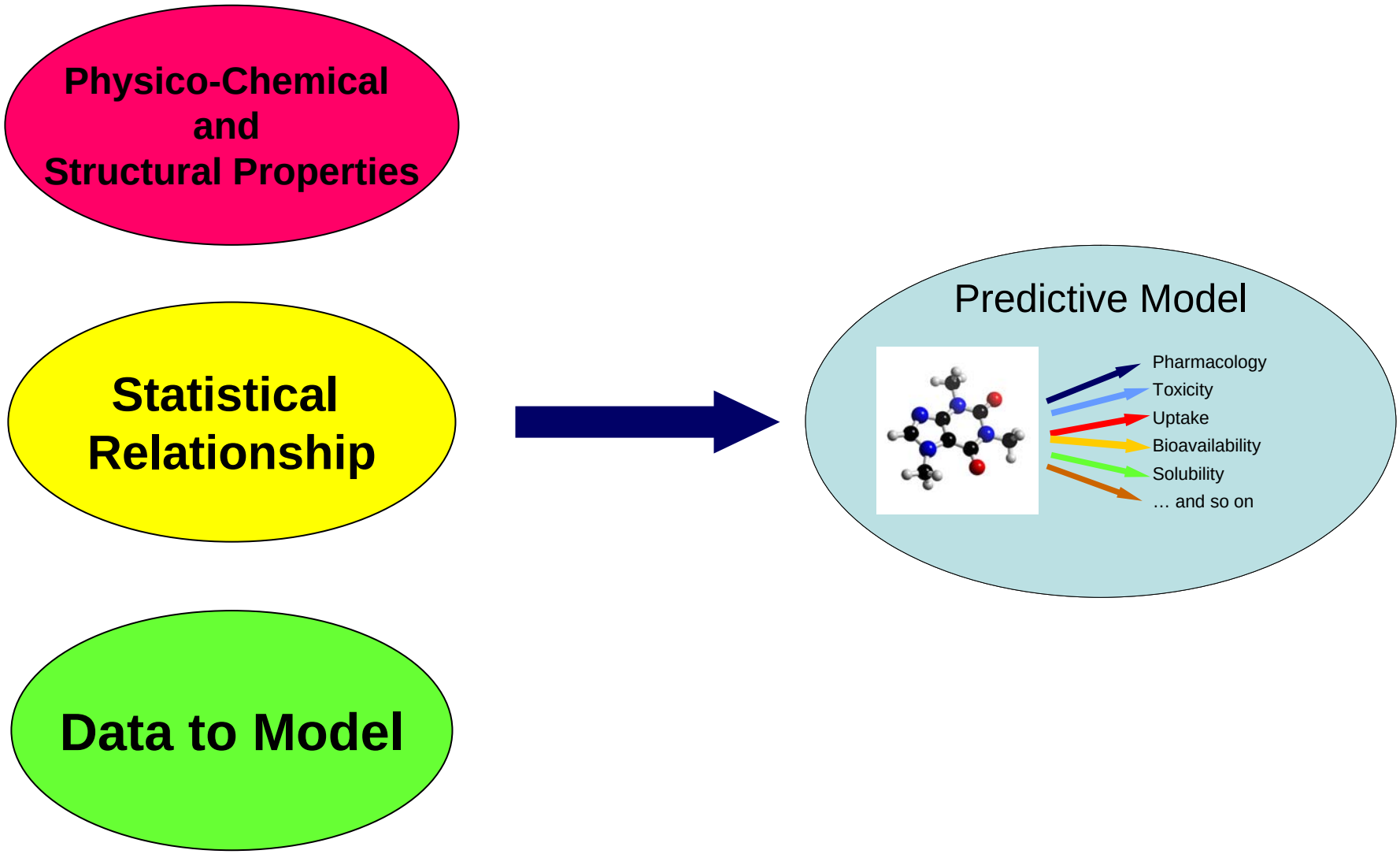

In Silico Predictions in Biology and Chemistry

Quantitative Structure-Activity Relationships (QSAR)

Quantitative Structure-Permeability Relationships (QSPR)

- **Predictive models need to be used correctly**
- **Requires expert knowledge**
- **A growth in interest due to REACH**

Why Predict?

- **Allows an estimation to made from chemical structure alone**
- **Savings in resources:**
  - **Time**
  - **Financial**
  - **Animals**
- **Understanding of mechanism of action**
- **Allows for rational product development**

Modelling Skin Permeation:
Data Requirements

- **High quality data for a suitable endpoint or measurement**
- **Models work best with steady state systems**
- **K_p and J_{max}**

Algorithms from Calculating Permeability Coefficient (K_p)

	MW < 150Da	MW > 150Da
log P < 0.5	log Kp = -3	log Kp = -5
0.5<log P<3.0	log Kp = log P - 3.5	
log P > 3.0	log Kp = -0.5	
log P > 3.5		log Kp = -1.5

Adapted from Flynn (1990)

K_p for Some Aliphatic Alcohols

	log K_p
Methanol	-3.30
Ethanol	-3.10
Propanol	-2.92
Butanol	-2.60
Pentanol	-2.22
Hexanol	-1.89
Heptanol	-1.49
Octanol	-1.28
Nonanol	-1.22
Decanol	-1.09

K_p and log P

	log K_p	log P
Methanol	-3.30	-0.76
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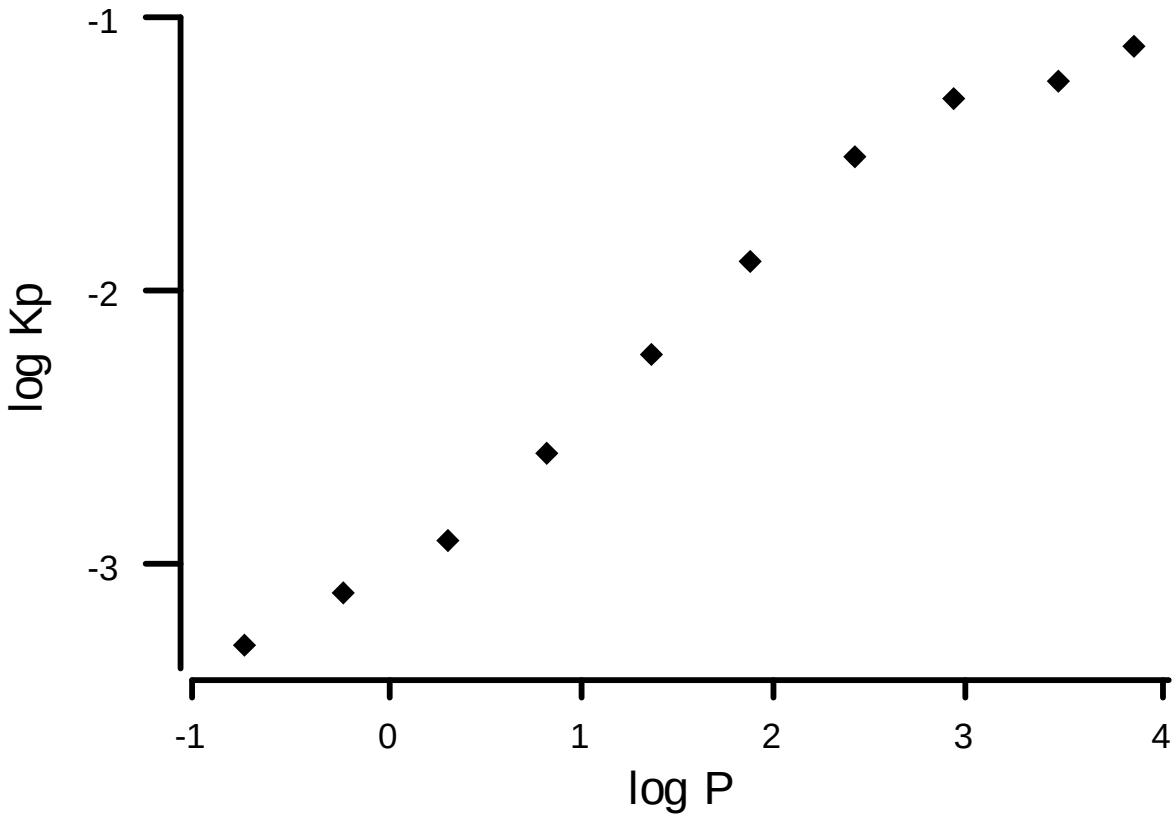
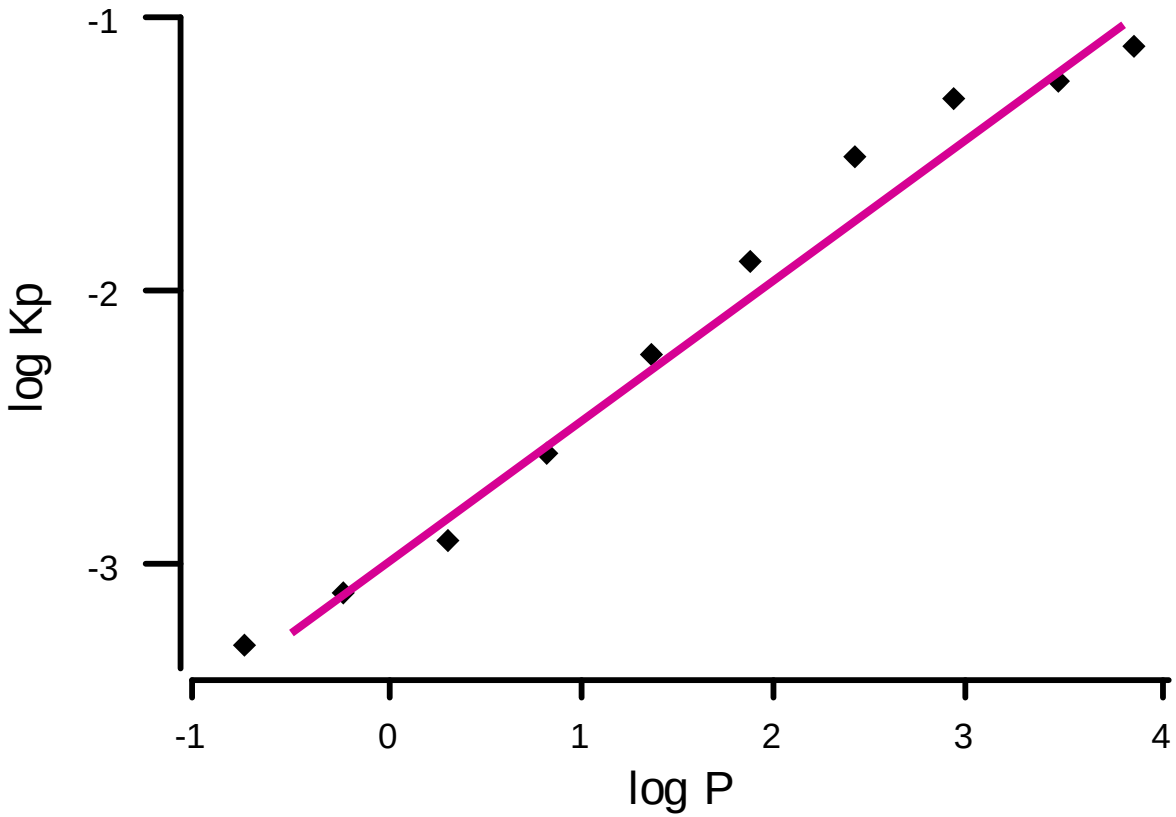

-1
-2
-3
log Kp
-1
0
1
2
3
4
log P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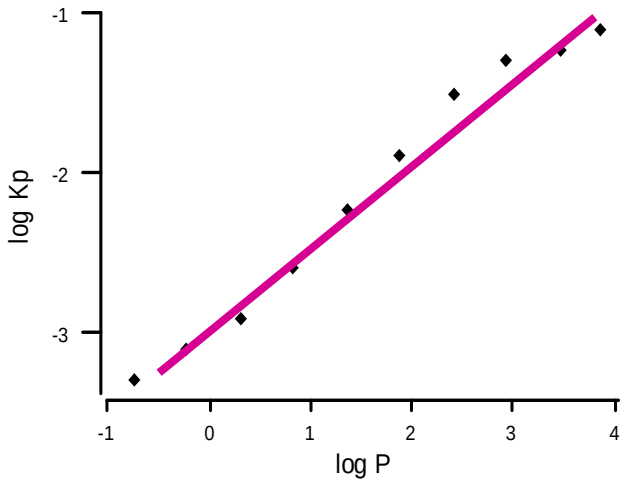
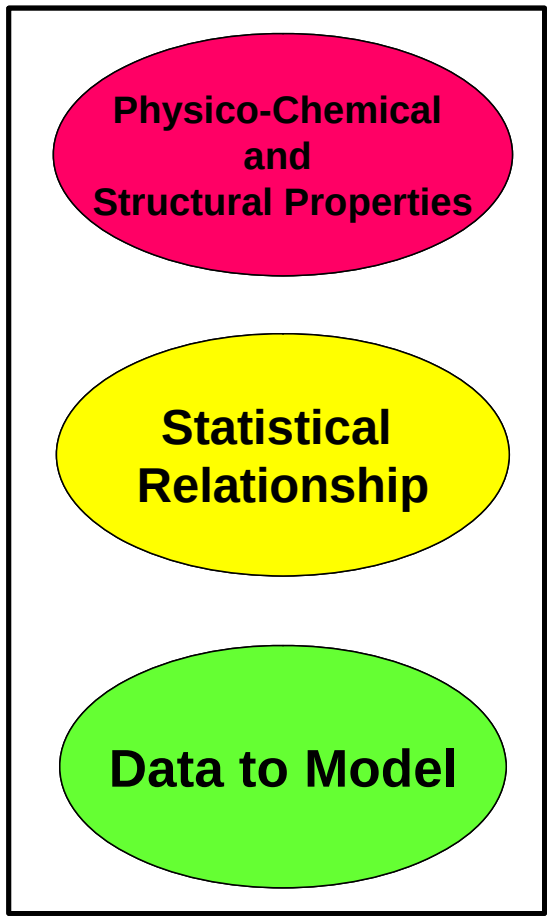
QSAR for Kp for Alcohols

$$\log K_p = 0.54 \log P - 2.88$$





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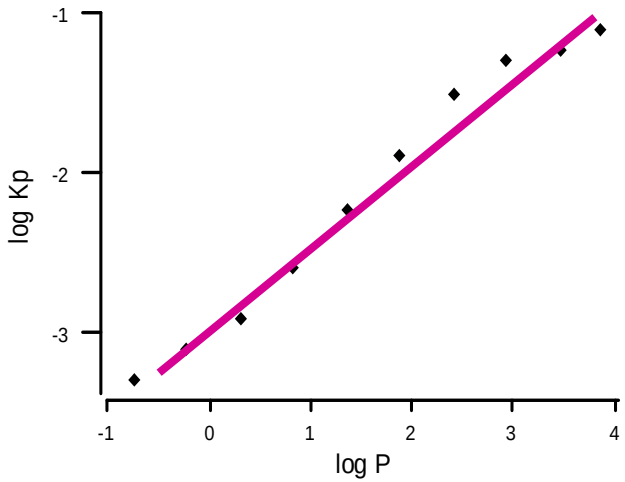

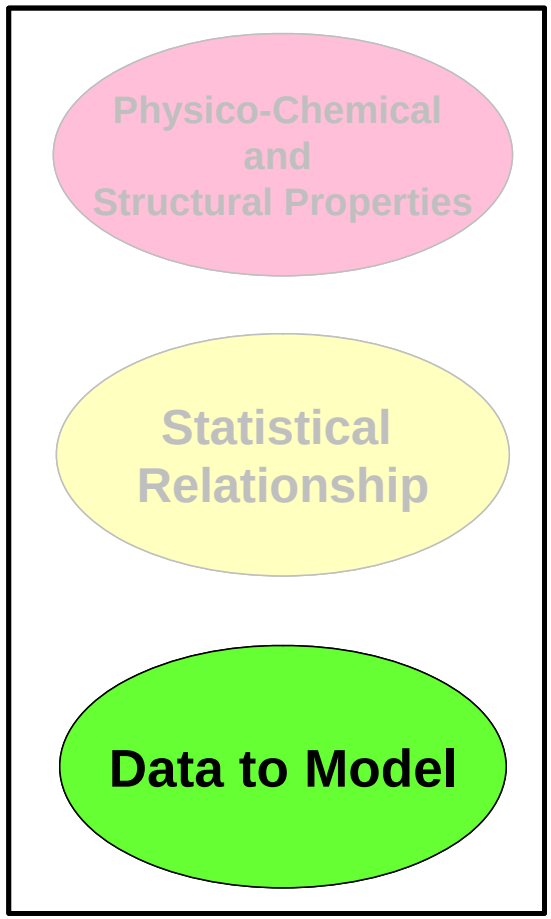

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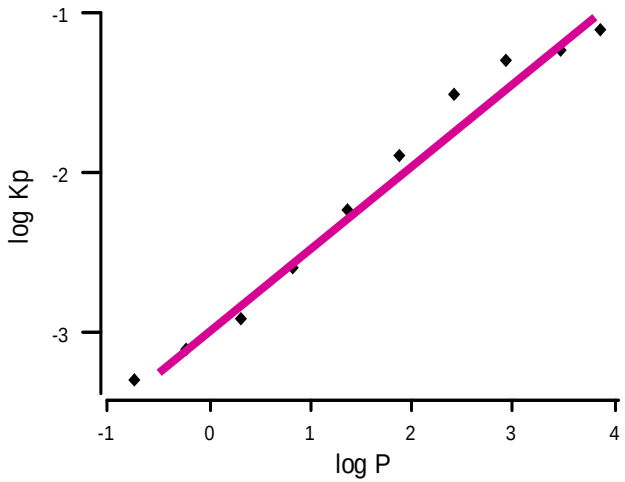

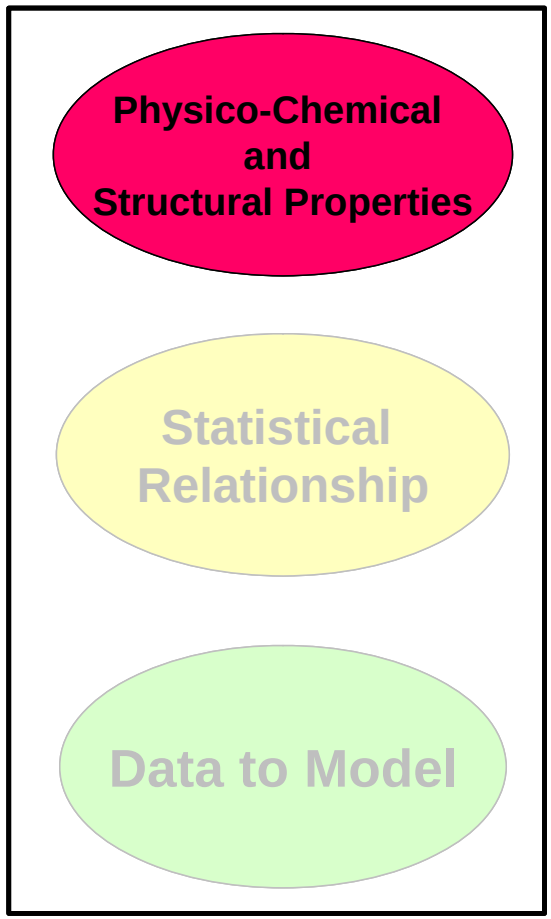

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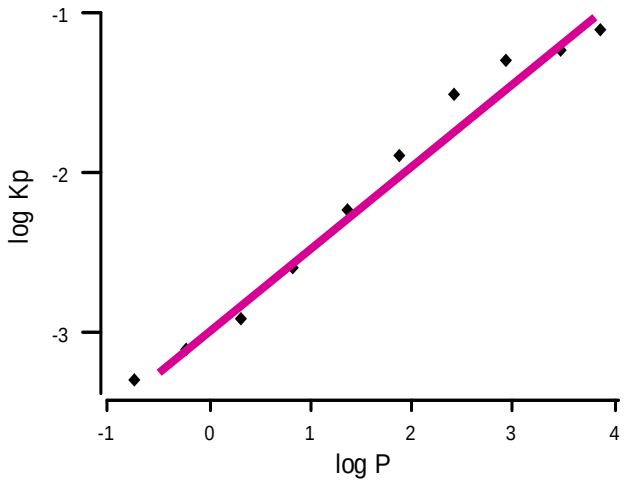

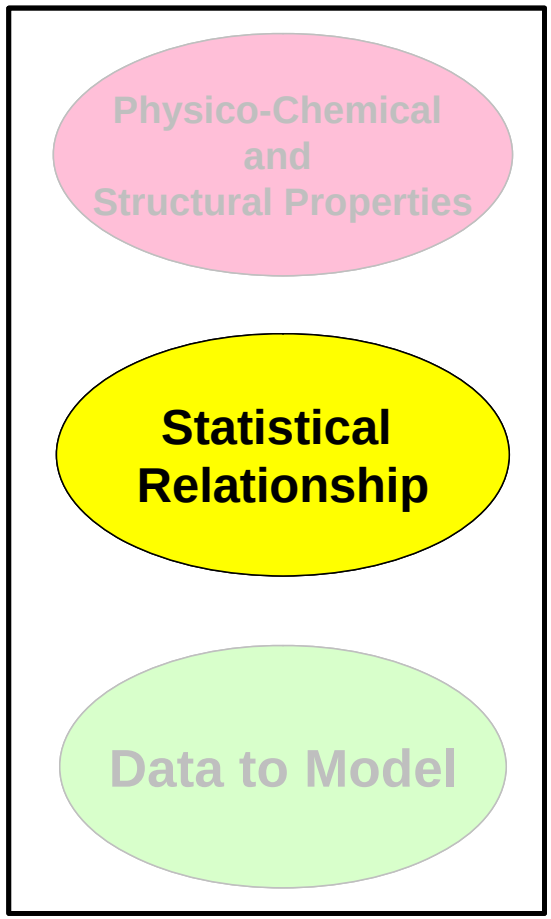

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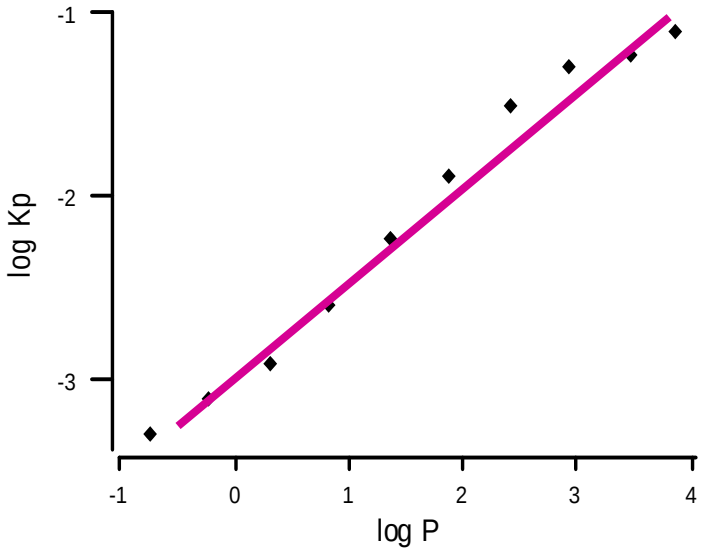

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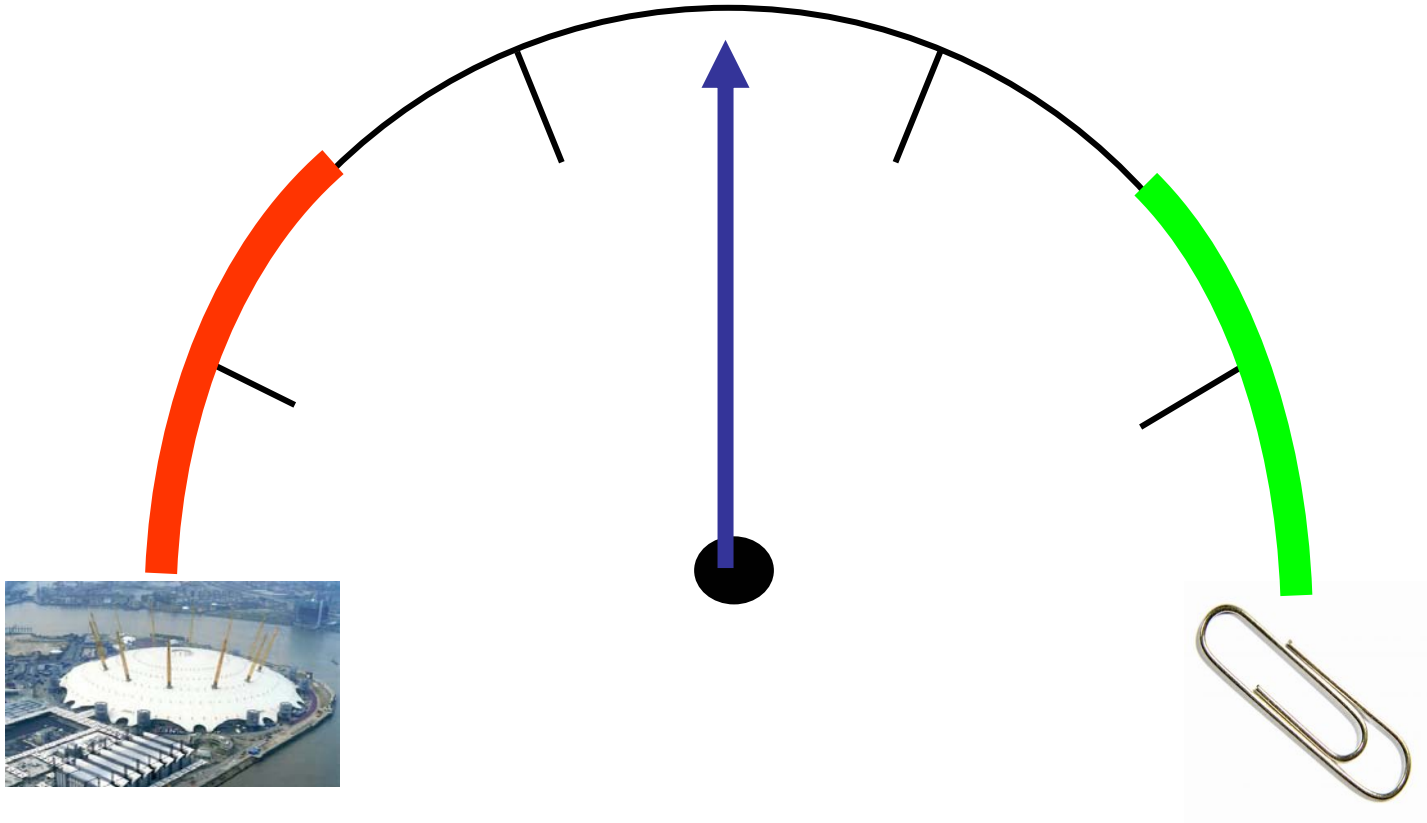
Useful or Useless: Usefullessness-o-Meter



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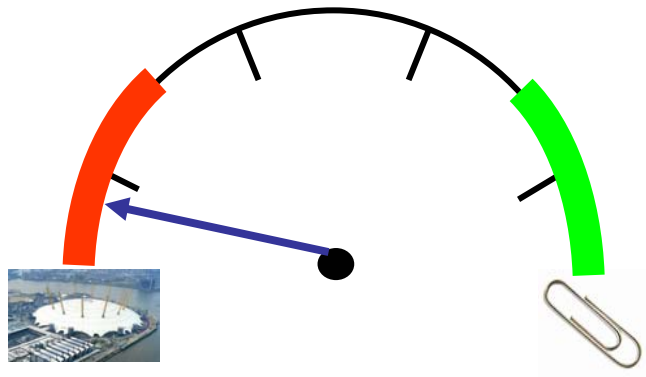

General Equation for Skin Permeability

Log Kp = Hydrophobicity - Molecular Size

Potts and Guy Model:

Log Kp = 0.71 log P - 0.0061 MW - 6.3

n = 93 r^2 = 0.67

Potts RO, Guy RH (1992) *Pharm Res* 9: 663

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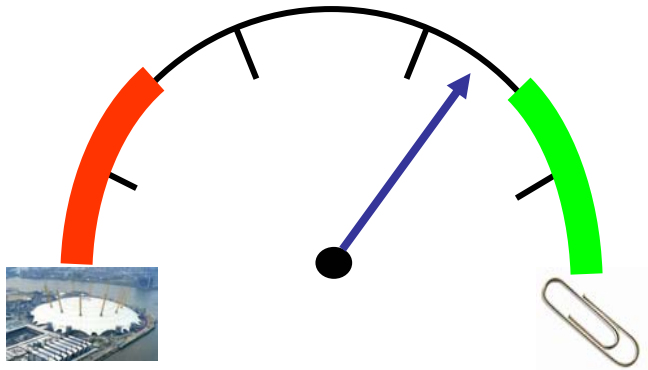

Variations on a Theme

log Kp = 0.65 log P - 0.0060 MW

- 0.62 ABSQon - 0.31 SsssCH - 2.3

n = 143 r^2 = 0.90 s = 0.35

r^2 = 0.79 with log P and MW alone

Patel H et al (2002) *Chemosphere* 48: 603-613

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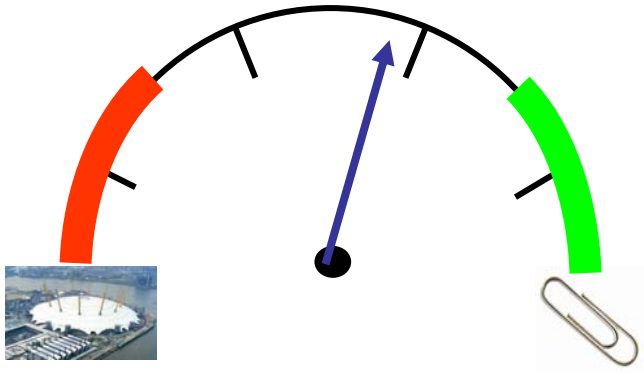


Dermwin

http://www.epa.gov/opptintr/exposure/pubs/episuite.htm

Dermwin v1.42

File Edit Functions BatchMode ShowStructure Help

Previous | Get User | Save User | CAS Input | Calculate

Enter SMILES: Nc1ccc(CC)cc1

Enter NAME:

Enter Event Duration [hrs]: 0.25

Enter Water Conc [mg/cm3]: 0

[Optional] Enter Log Kow :

[Optional] Enter Kp [cm/hr]:

Structure

File Edit Structure Help

Results

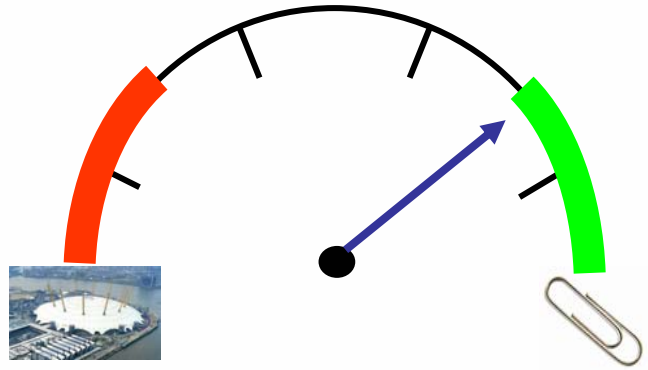
Print Save Results Copy Remove Window Help

Kp (est): 0.00856 cm/hr

```
SMILES : Nc1ccc(CC)cc1
CHEM   :
MOL FOR: C8 H11 N1
MOL WT : 121.18
------------------------------ Dermwin v1.42 ----------------------------------
Log Kow  (estimated)  :  2.11
Log Kow (experimental):  1.96   (used in Kp calculations)
    Cas No: 000589-16-2
    Name  : p-Ethylaniline
    Refer : Hansch,C et al. (1995)

GENERAL Equation:   log Kp = -2.72 + 0.71 log Kow - 0.0061 MW
    Kp (predicted): 8.56e-003  cm/hr

Dermally Absorbed Dose per Event:
   Water Conc (mg/cm3): 2.1  (estimated by program)
   Event Duration (hr): 0.25
   DA(event):  0.0045 mg/cm2-event (using Fick's first law)
   DA(event):  0.017 mg/cm2-event (using eqn 5.20 & 5.21)
                (tau = 0.48 hr,  t* = 1.2 hr)
```



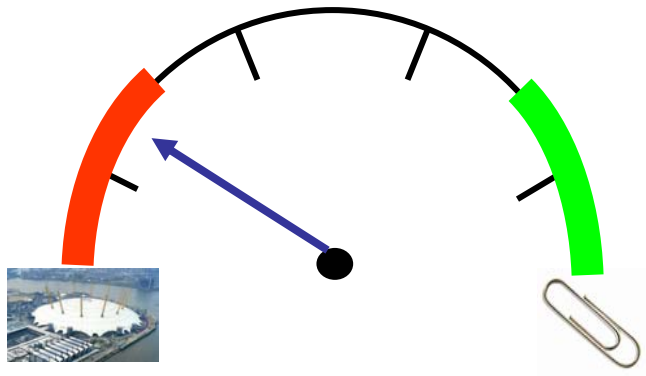
Many Attempts to Predict Percutaneous Absorption

- **Flynn dataset**
  - **Flynn GL (1990)**
- **Expanded datasets**
  - **Wilschut A et al (1995) *Chemosphere* 30: 1275**
- **Isolated datasets**

- **Reviews:**
  - **Moss G et al (2002) *Toxicol in Vitro* 16: 299**
  - **Geinoz S et al (2004) *Pharm Res* 21: 83**

Evaluation and Possible Validation of QSPRs

- **External validation suggests:**
  - **QSARs for Kp most successful for neat liquids**
  - **further data required**
- **Usefulness is context dependent**
  - **is there a context where a prediction of K_p from an aqueous solution at infinite dose is relevant?**

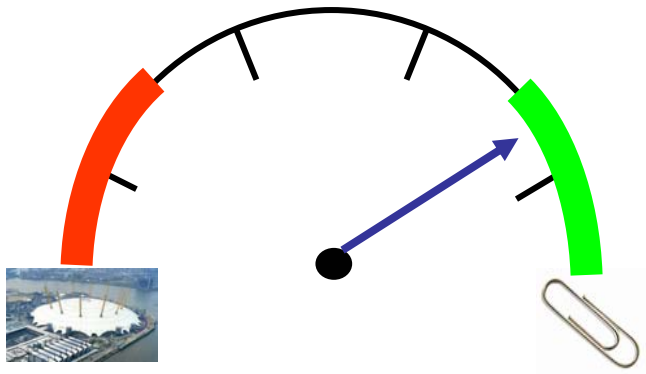


Modelling Flux

$$\log J_{max} = - 0.0141\ MW - 4.52$$

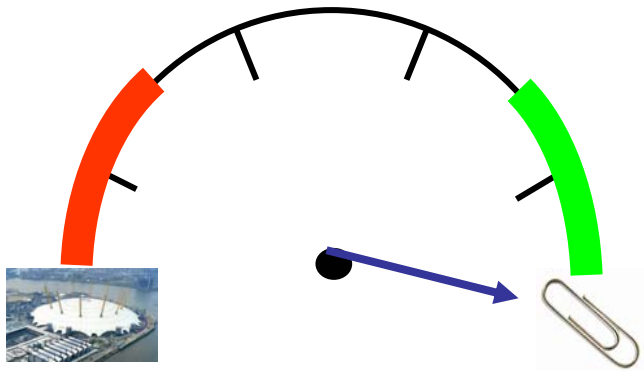
$$n = 278 \quad r^2 = 0.69$$

Magnusson BM et al (2004) *J. Invest. Dermatol*. 122: 993-999



What Would be *Really* Useful

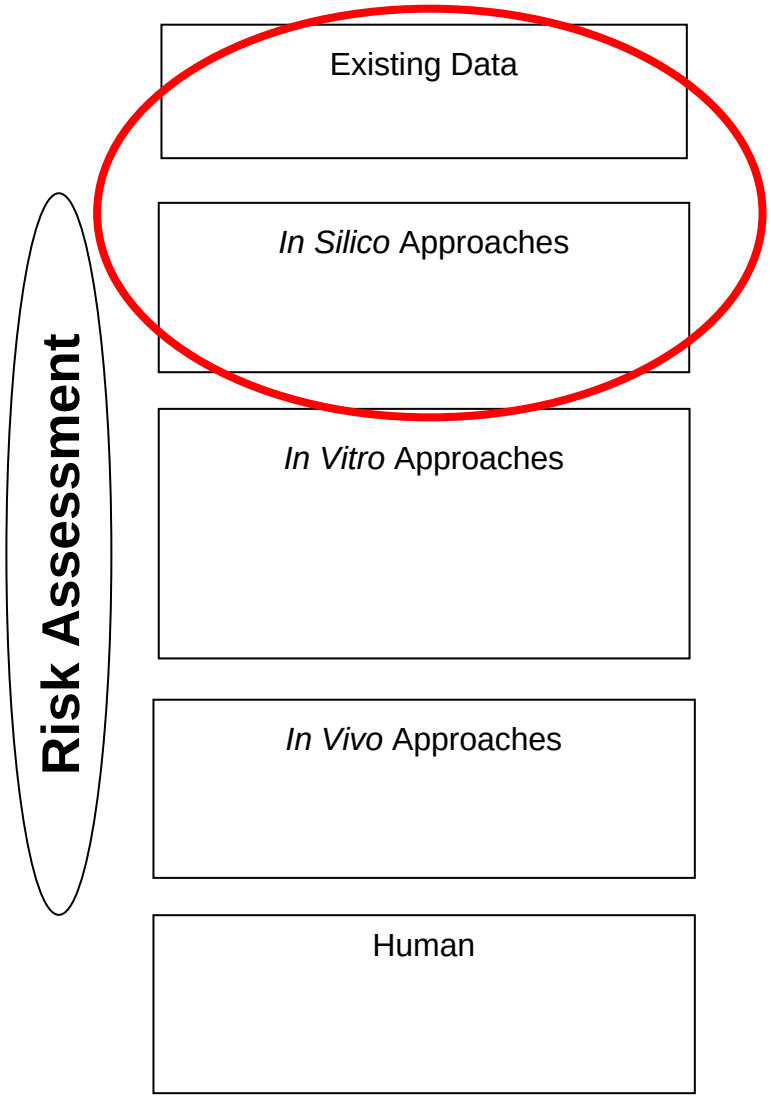
- **Predictions taking account of solubility, vehicle, occlusion**
- **Finite dose**
- **Skin type**
- **Formulation**
- **Exposure scenario**

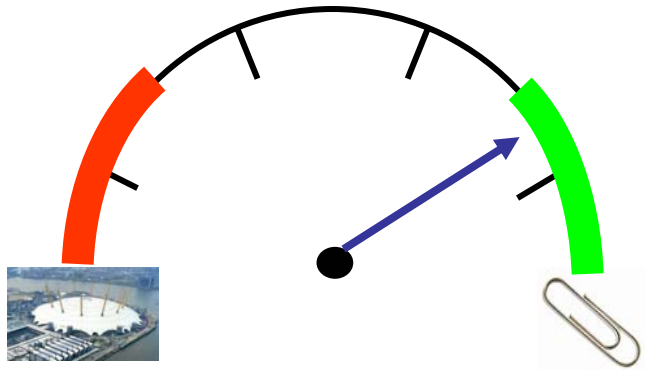


Structure-Permeability Relationships: Read Across

- **A single, “ultimate”, QSPR is not a reality (for the moment)**
- **Could we break it down into components and combine together intelligently?**
- **Read across will become an increasingly common approach for toxicity prediction**
  - **Why not permeability read-across?**

Implementation of Alternative Technologies: Integrated (or Intelligent?) Testing Strategies





Conclusions

- **QSPRs are attractive, but restricted in use**
- **Automated models are available**
- **For complete “usefulness”, considerable of other factors may be required**