



# **The distribution of compounds between blood and various biological tissues**

Presented by Adam Ibrahim

# Plan

- Aim
- Abraham equations
- New Abraham equations for VOCs from air to tissue and distribution from blood to tissue
- New Abraham equations for drug blood tissue distribution
- Conclusion

## Aim

To construct equations for general correlations for compounds including volatile organic compounds and for neutral drug species

# The equation

Coefficients relating  
to interaction properties of solvent phase

$$(1) \text{ SP} = c + e.E + s.S + a.A + b.B + l.L$$

$$(2) \text{ SP} = c + e.E + s.S + a.A + b.B + v.V$$

Solute property

Descriptors relating to  
compound properties

1. Gas-solvent partition phase

2. Solvent-solvent partition phase

# The descriptors

Equation for gas-solvent phase

$$SP = c + e.E + s.S + a.A + b.B + l.L$$

Equation for solvent-solvent phase

$$SP = c + e.E + s.S + a.A + b.B + v.V$$

**E** Excess molar refraction

**S** Polarisability/dipolarity

**A** Hydrogen bond acidity

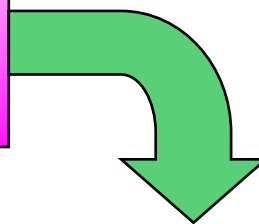
**B** Hydrogen bond basicity

**V** Mc Gowan volume

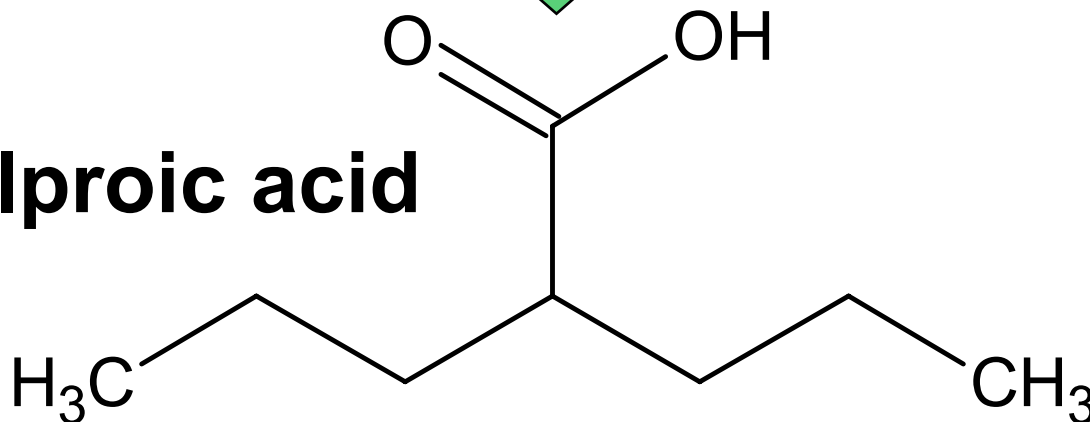
**L** Gas-hexadecane partition coefficient

# Descriptor 'I' for drug compounds containing carboxylic acids groups

Carboxylic acid group

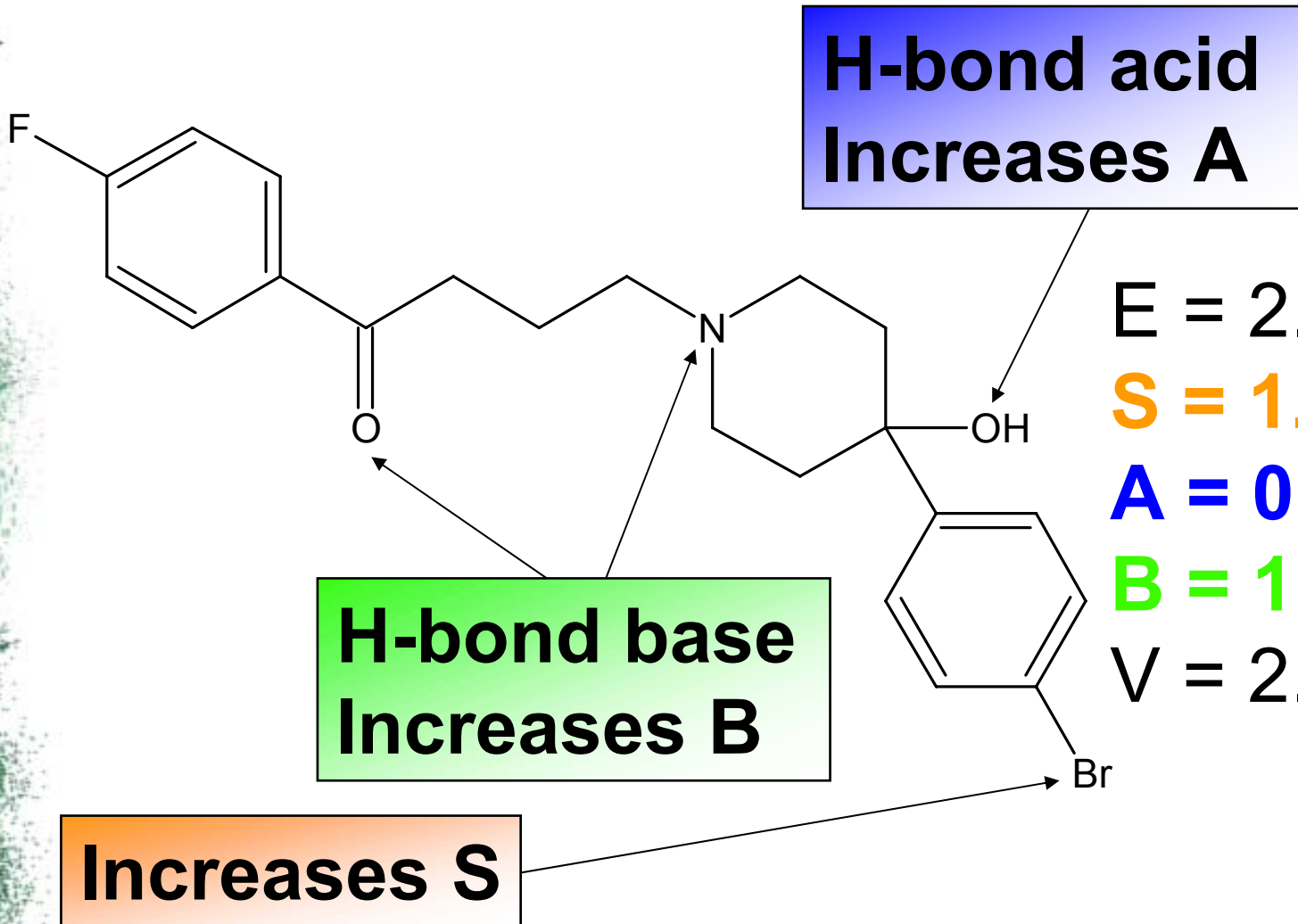


**E.g. Valproic acid**

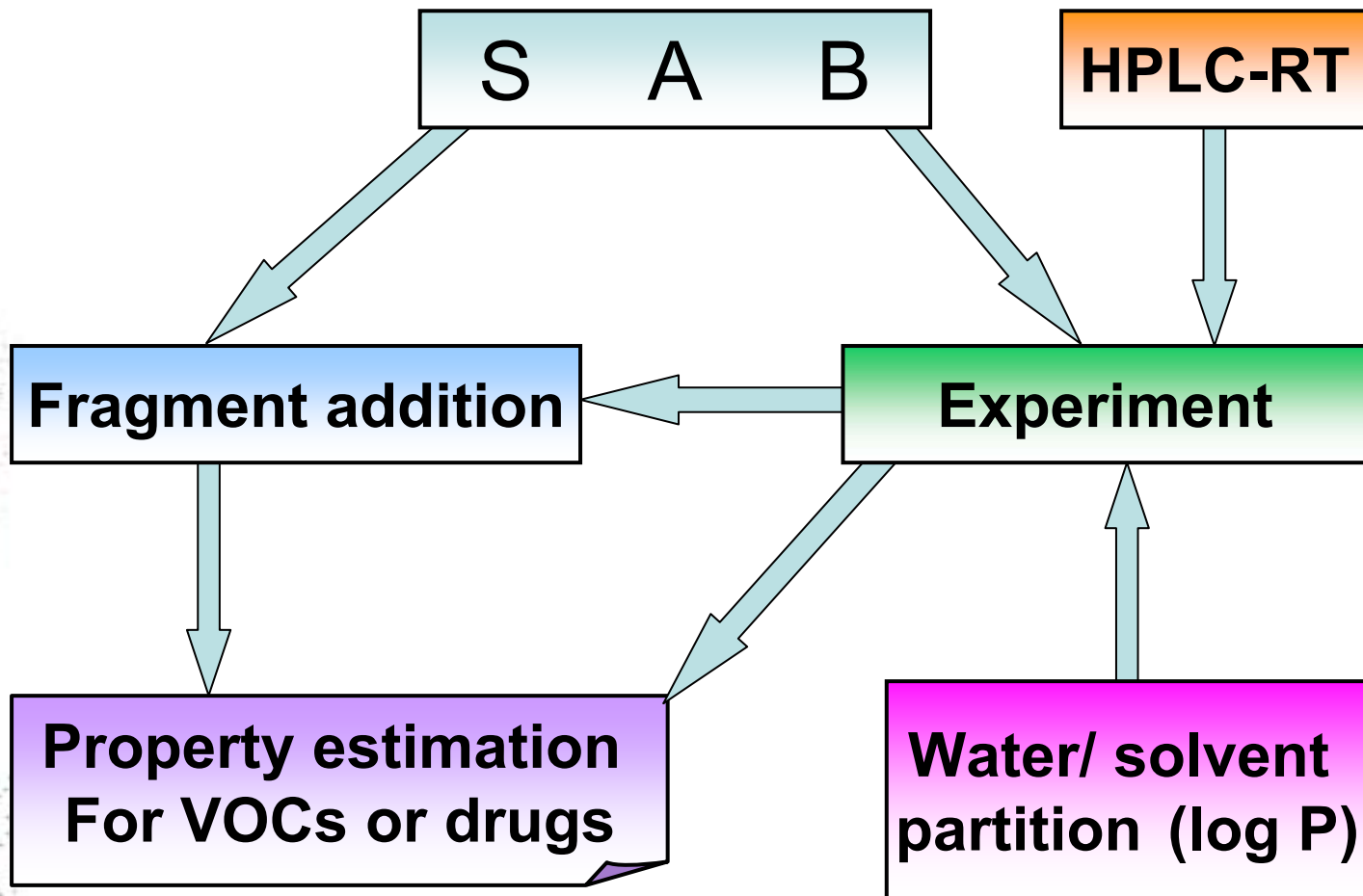


**Here descriptor 'I' = 1**

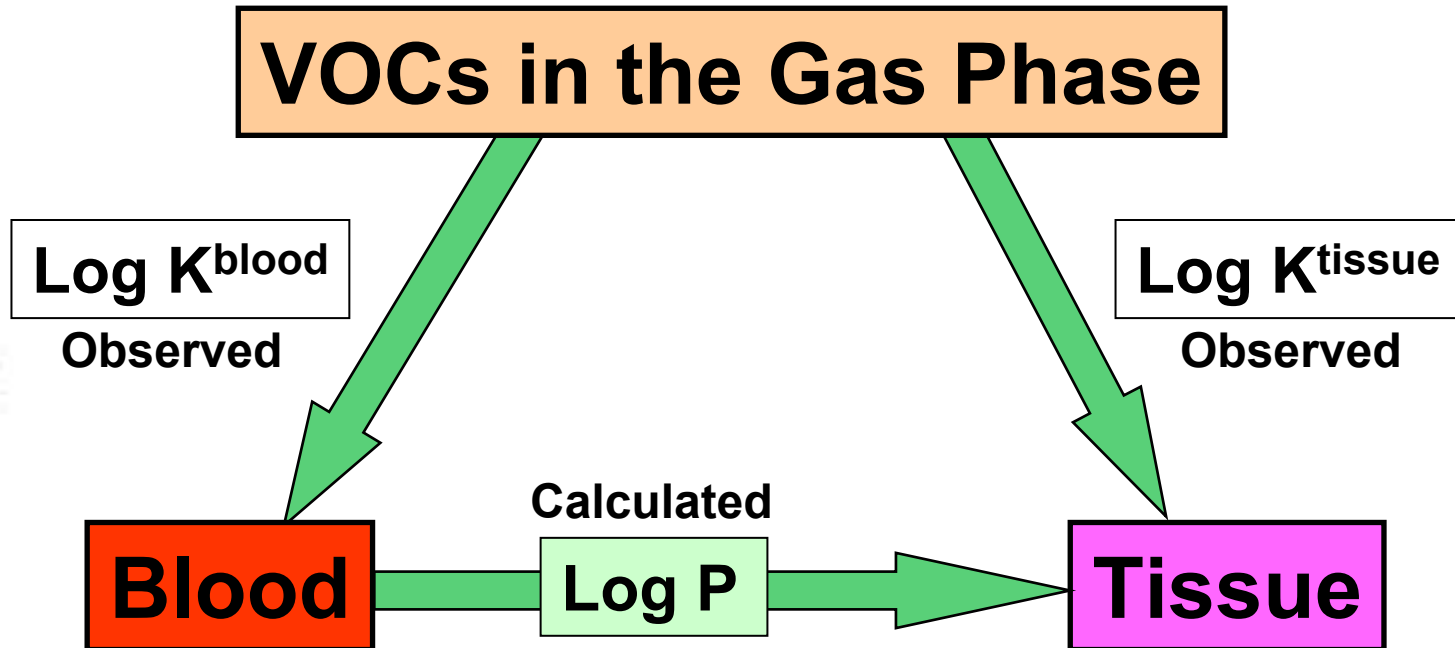
# Anti-psychotic drugs e.g. Bromperidol



# Descriptor estimation



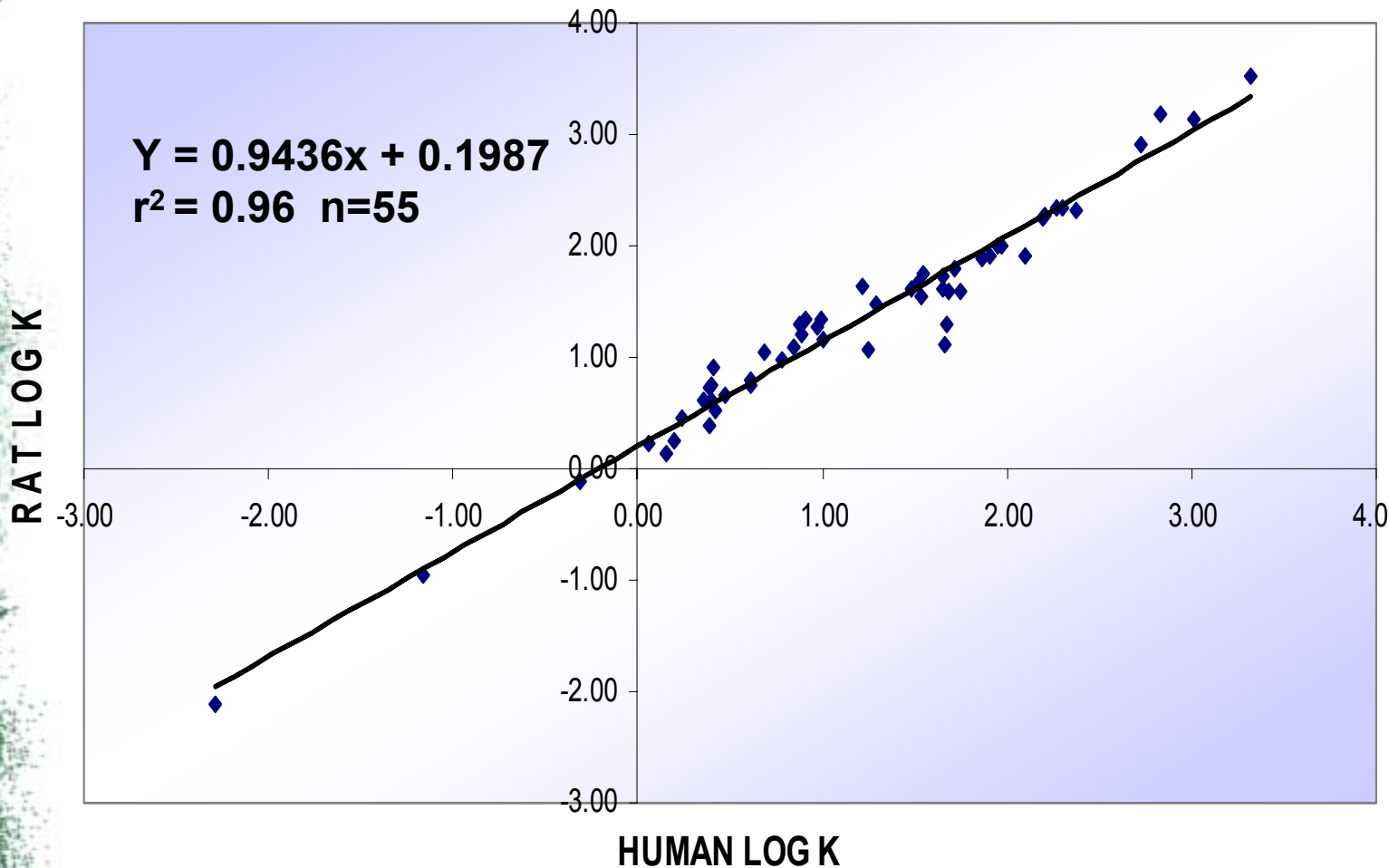
# How to get drug blood-tissue distribution for VOCs?



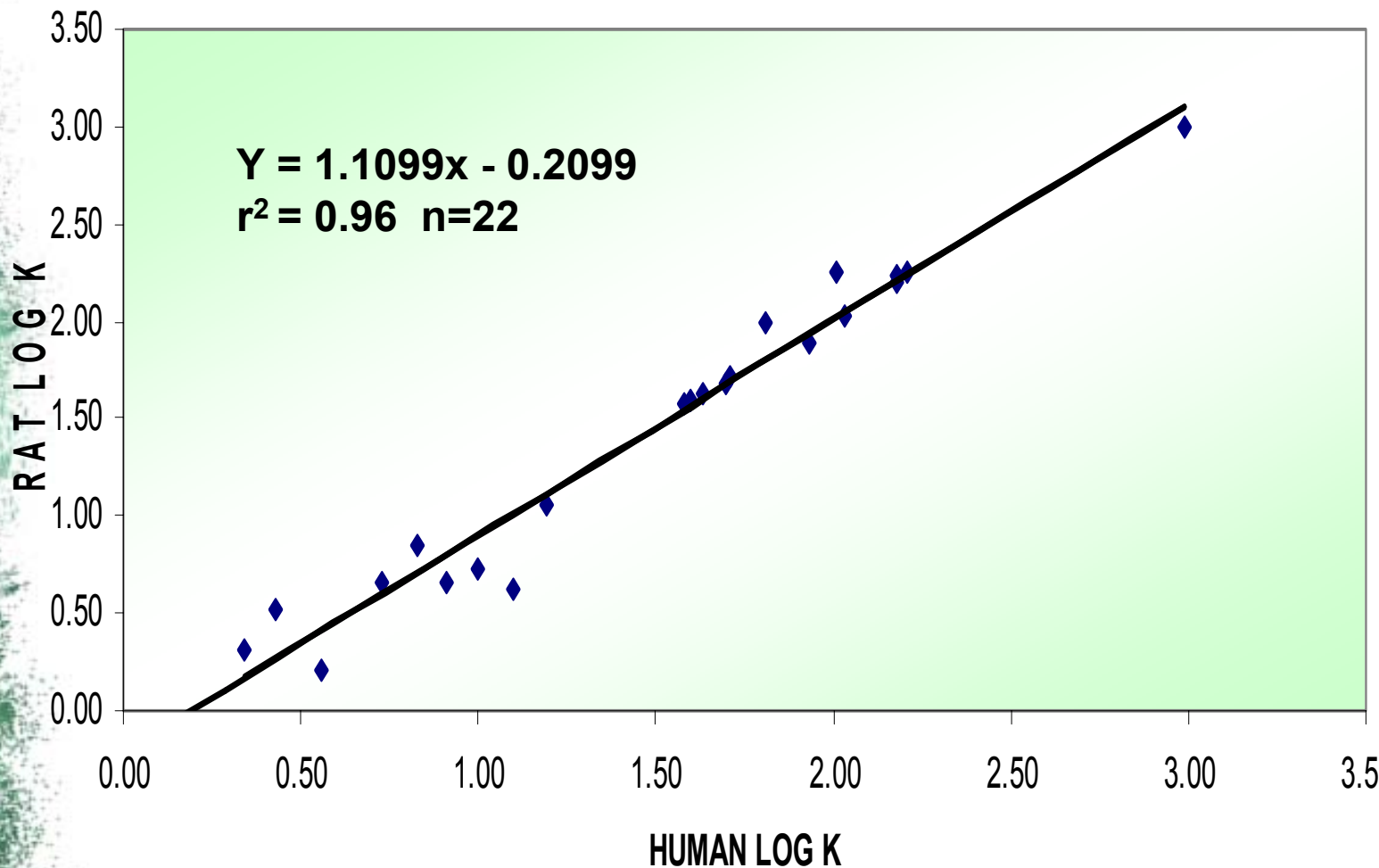
$$K = \frac{[\text{conc. of solute in a tissue or blood}]}{[\text{conc. of solute in the gas phase}]}$$

$$\text{Log } P_{(t:b)} = \log K_{\text{tissue}} - \log K_{\text{blood}}$$

# Human verses rat plot for air/blood log K for VOCs



# Human verses rat plot for air/tissue log K for VOCs



# Gas-tissue phase distribution for VOCs, as log K

## Log air-blood

$$\text{Log AB} = -1.17 + 0.34\text{E} + 1.22\text{S} + 3.83\text{A} \\ + 2.52\text{B} + 0.39\text{L}$$

$$n = 194 \quad r^2 = 0.95 \quad \text{s.d.} = 0.29 \quad F = 736.96$$

## Log air-lung

$$\text{Log AL} = -1.29 + 0.58\text{E} + 0.98\text{S} + 3.70\text{A} \\ + 3.08\text{B} + 0.44\text{L}$$

$$n = 37 \quad r^2 = 0.97 \quad \text{s.d.} = 0.25 \quad F = 216.37$$

# Gas-tissue phase distribution for VOCs, as log K

<b>PHASE</b>	<b>n</b>	<b>r<sup>2</sup></b>	<b>Standard deviation</b>
<b>BLOOD</b>	<b>194</b>	<b>0.95</b>	<b>0.29</b>
<b>PLASMA</b>	<b>36</b>	<b>0.98</b>	<b>0.25</b>
<b>BRAIN</b>	<b>76</b>	<b>0.94</b>	<b>0.30</b>
<b>MUSCLE</b>	<b>109</b>	<b>0.95</b>	<b>0.25</b>
<b>LUNG</b>	<b>37</b>	<b>0.97</b>	<b>0.25</b>
<b>LIVER</b>	<b>116</b>	<b>0.92</b>	<b>0.26</b>
<b>KIDNEY</b>	<b>72</b>	<b>0.92</b>	<b>0.32</b>
<b>HEART</b>	<b>25</b>	<b>0.96</b>	<b>0.17</b>
<b>FAT</b>	<b>124</b>	<b>0.95</b>	<b>0.21</b>
<b>URINE</b>	<b>47</b>	<b>0.91</b>	<b>0.36</b>
<b>OLIVE OIL</b>	<b>221</b>	<b>0.97</b>	<b>0.25</b>
<b>SALINE (0.9%)</b>	<b>132</b>	<b>0.96</b>	<b>0.33</b>

# Blood-tissue distribution, as log P for VOCs

## Log blood-brain

$$\text{Log BB} = -0.11 + 0.15E - 0.39S - 0.34A \\ - 0.62B + 0.87V$$

$$n = 72 \quad r^2 = 0.84 \quad \text{s.d.} = 0.16 \quad F = 69.54$$

## Log blood-plasma

$$\text{Log BP} = -0.06 - 0.30E + 0.29S + 0.05A \\ + 0.34B - 0.24V$$

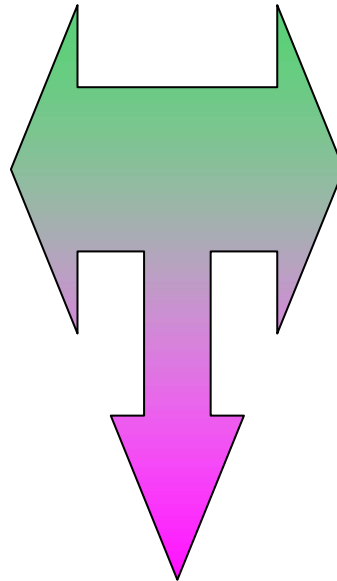
$$n = 32 \quad r^2 = 0.67 \quad \text{s.d.} = 0.08 \quad F = 10.42$$

# Blood-tissue distribution, as log P for VOCs

<b>PHASE</b>	<b>n</b>	<b>r<sup>2</sup></b>	<b>Standard deviation</b>
<b>PLASMA</b>	<b>32</b>	<b>0.67</b>	<b>0.08</b>
<b>BRAIN</b>	<b>72</b>	<b>0.84</b>	<b>0.16</b>
<b>MUSCLE</b>	<b>101</b>	<b>0.65</b>	<b>0.20</b>
<b>LUNG</b>	<b>35</b>	<b>0.51</b>	<b>0.12</b>
<b>LIVER</b>	<b>111</b>	<b>0.59</b>	<b>0.22</b>
<b>KIDNEY</b>	<b>71</b>	<b>0.79</b>	<b>0.19</b>
<b>HEART</b>	<b>25</b>	<b>0.83</b>	<b>0.14</b>
<b>FAT</b>	<b>120</b>	<b>0.84</b>	<b>0.31</b>

VOCs data combined with drug data to give rise to a new models for drug blood tissue distribution

**Environmental  
VOCs data**



**Pharmaceutical  
Drugs data**

**Models for drug blood tissue  
distribution for small and large solutes**

# Equations for VOCs + drugs combined

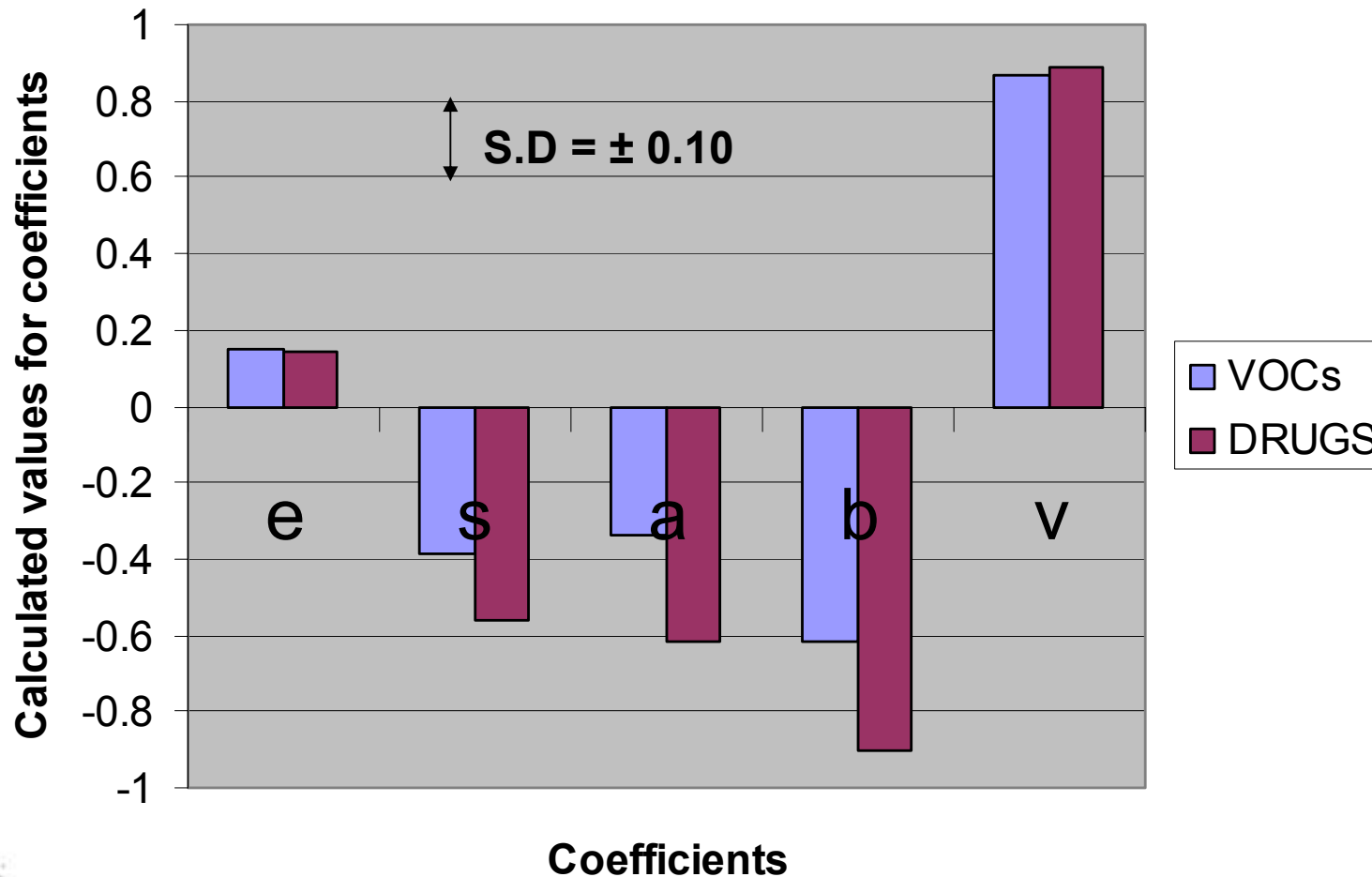
## Log blood-brain

$$\text{Log BB} = 0.01 + 0.18E - 0.49S - 0.57A \\ - 0.69B + 0.83V - 1.02I \\ n = 178 \quad r^2 = 0.77 \quad \text{s.d.} = 0.32 \quad F = 96.23$$

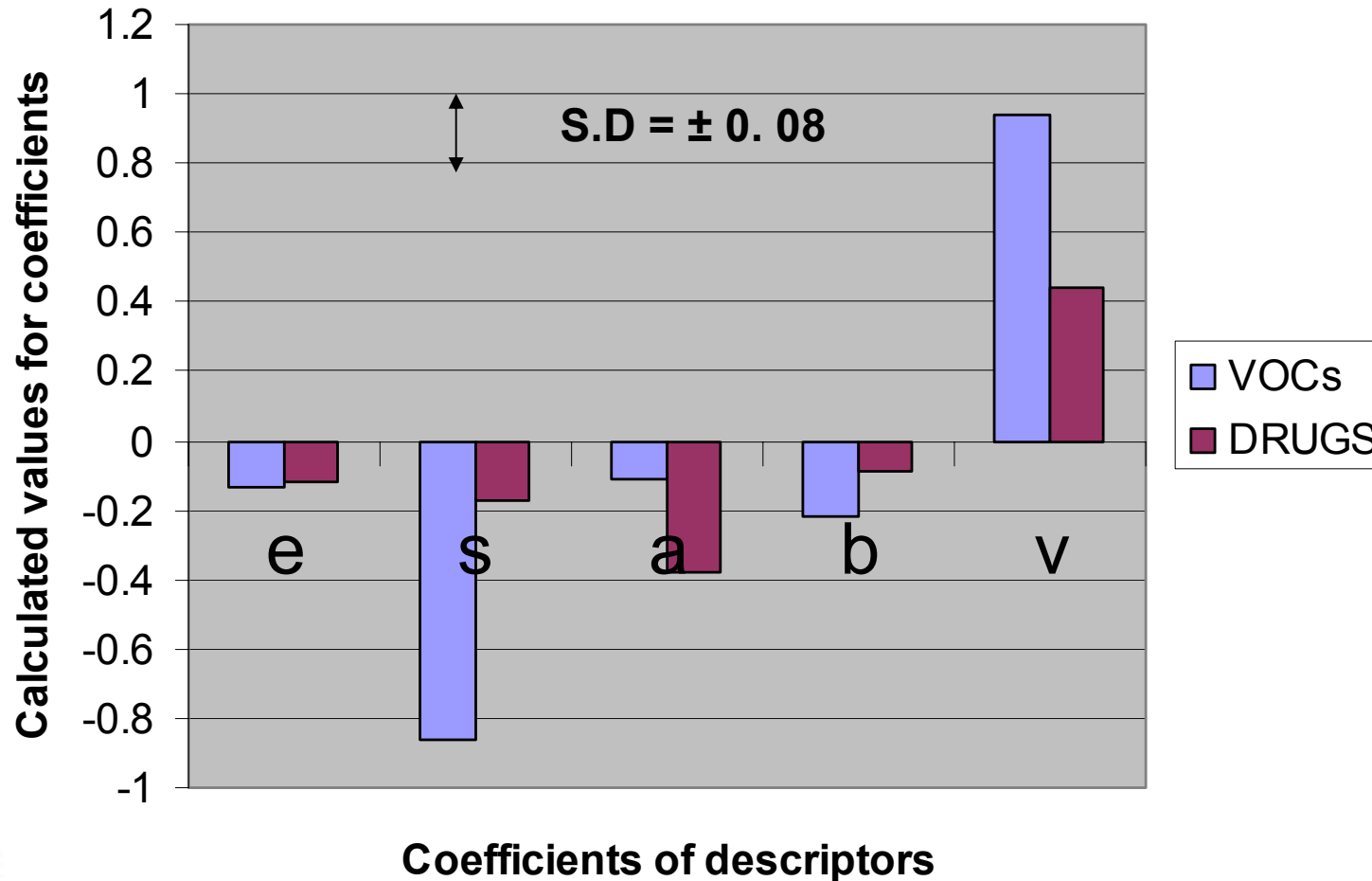
## Log blood-muscle

$$\text{Log BB} = -0.21 - 0.10E - 0.34S - 0.15A \\ - 0.17B + 0.65V - 1.16I \\ n = 151 \quad r^2 = 0.60 \quad \text{s.d.} = 0.24 \quad F = 36.56$$

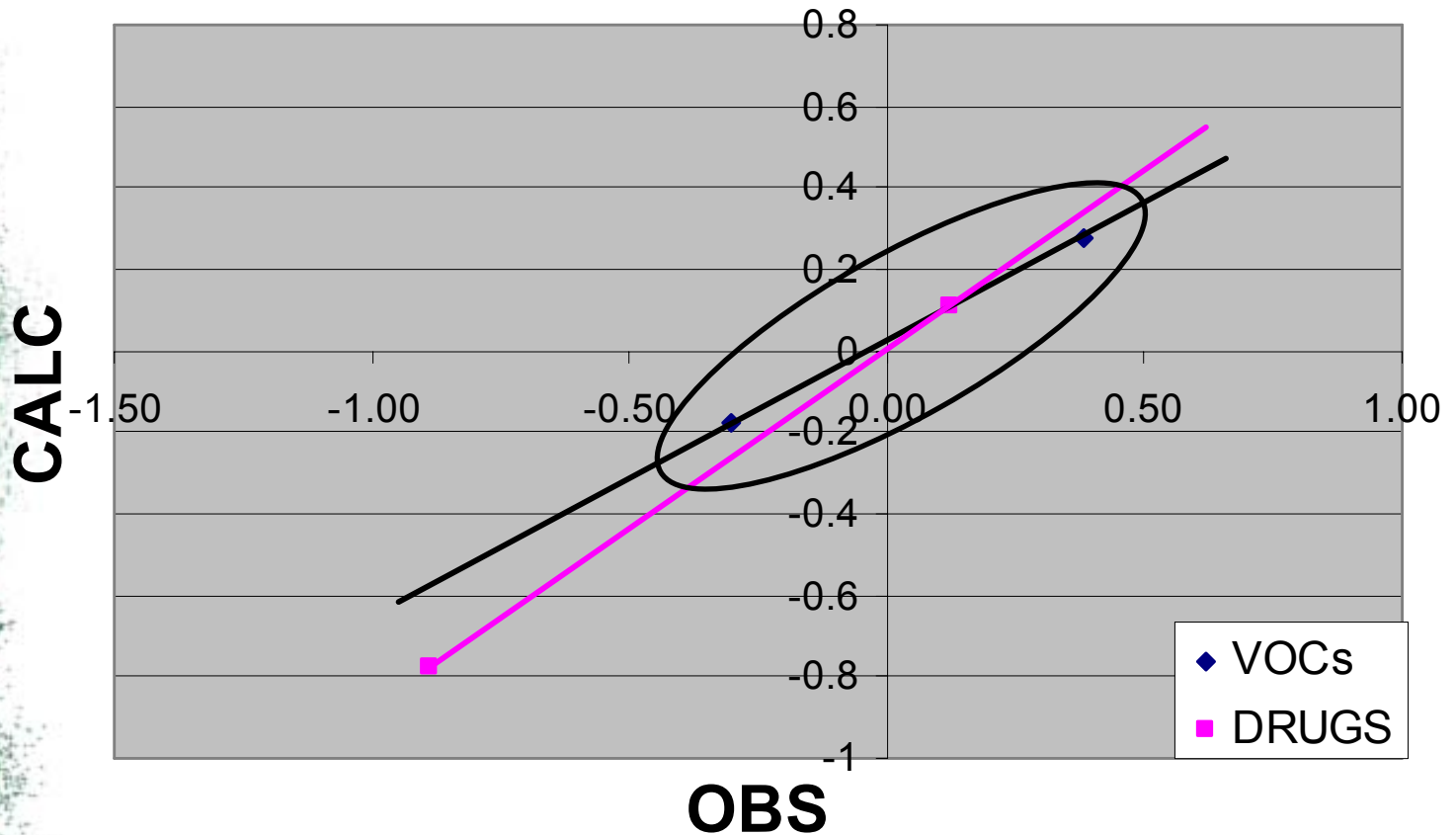
# The coefficients for VOCs and drugs fall within the same standard deviation for blood brain?



# The coefficients for VOCs and drugs don't fall within the same standard deviation for blood muscle?



# Comparisons of two slopes for blood muscle distributions



# How do fits for drugs compare with the fits from VOCs + drugs in total?

<b>Equations for muscle</b>	<b>AAE</b>	<b>AE</b>
<b>Drugs</b>	<b>0.15</b>	<b>-0.02</b>
<b>VOCs + Drugs</b>	<b>0.18</b>	<b>0.00</b>

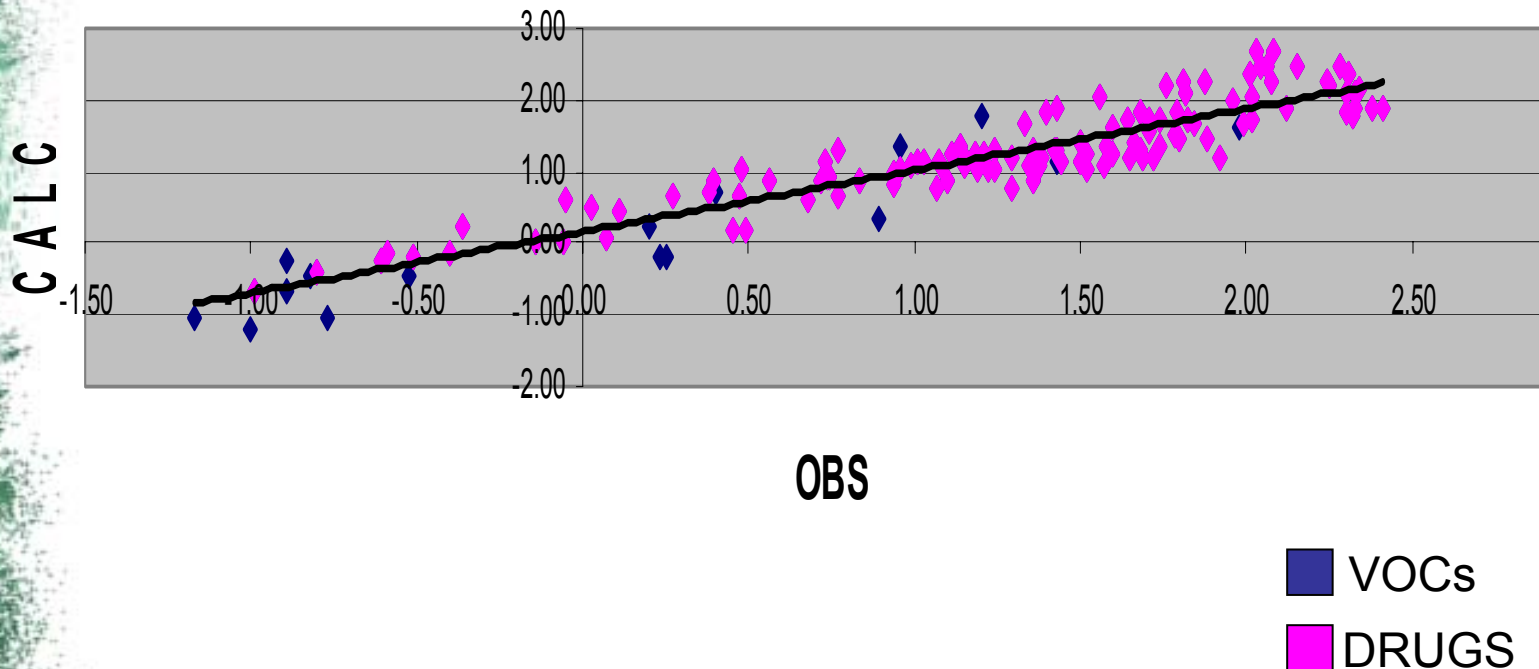
# Coefficients (drugs + VOCs) and the order of % adipose content

Phase	e	s	a	b	v
Fat	0.25	-0.16	-1.74	-1.94	1.37
Brain	0.18	-0.49	-0.57	-0.69	0.83
Heart	0.24	-0.42	0.05	-0.56	0.74
Liver	0.06	-0.20	-0.41	-0.08	0.52
Kidney	-0.02	-0.38	-0.20	-0.17	0.78
Muscle	-0.10	-0.34	-0.15	-0.17	0.65
Lung	-0.10	-0.10	-0.50	0.26	0.31
Water	0.58	2.55	3.81	4.84	-0.87

# Blood-fat phase distribution, as log P (combined VOCs+drugs)

$$\text{Log BF} = 0.59 + 0.25E - 0.16S - 1.74A \\ - 1.94B + 1.37V - 0.76I$$

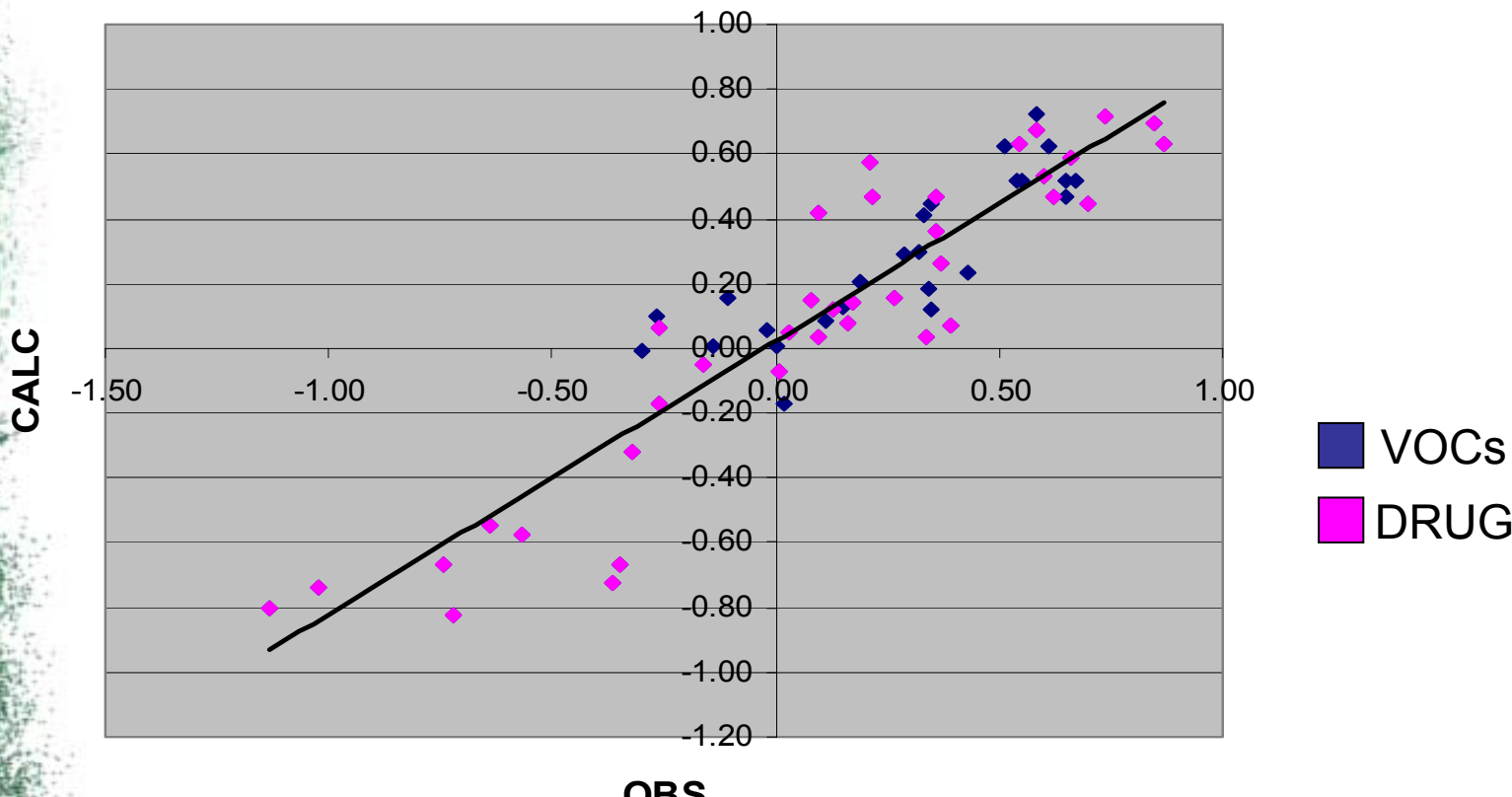
$n = 138$   $r^2 = 0.86$   $s.d. = 0.34$   $F = 133.28$



# Blood-heart phase distribution, as log P (combined VOCs+drugs)

$$\text{Log BH} = -0.19 + 0.24E - 0.42S + 0.05A \\ - 0.56B + 0.74V - 1.04I$$

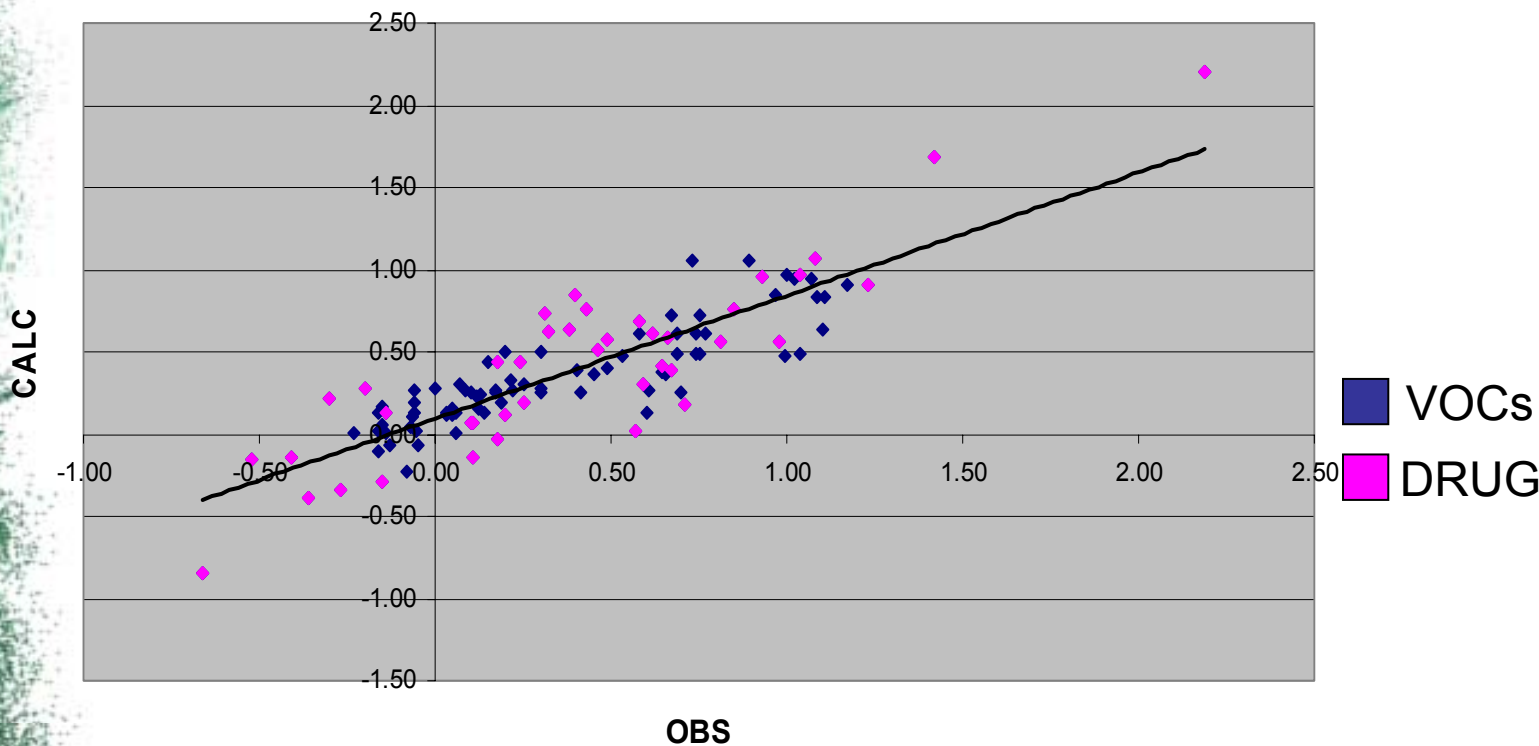
$n = 62$   $r^2 = 0.85$   $s.d. = 0.19$   $F = 50.25$



# Blood-kidney phase distribution, as log P (combined VOCs+drugs)

$$\text{Log BK} = -0.13 - 0.02E - 0.38S - 0.20A \\ - 0.17B + 0.78V - 0.49I$$

$n = 113$     $r^2 = 0.75$     $s.d. = 0.24$     $F = 52.51$



# Training set

## Kidney

$$\text{Log BK} = -0.08 + 0.03E - 0.45S - 0.14B + 0.72V - 0.56I$$

$$n = 56 \quad r^2 = 0.80 \quad \text{s.d.} = 0.25 \quad F = 33.59$$

# Test set

## Kidney

$$n = 57 \quad \text{s.d.} = 0.26 \quad \text{AAE} = 0.20 \quad \text{AE} = -0.02$$

# Blood-tissue phase distribution, as log P (VOCs+drugs)

<b>PHASE</b>	<b>n</b>	<b>r<sup>2</sup></b>	<b>Standard deviation</b>
<b>PLASMA</b>	39	0.61	0.08
<b>BRAIN</b>	178	0.77	0.32
<b>MUSCLE</b>	151	0.60	0.24
<b>LUNG</b>	82	0.77	0.25
<b>LIVER</b>	158	0.62	0.26
<b>KIDNEY</b>	113	0.75	0.24
<b>HEART</b>	62	0.85	0.19
<b>FAT</b>	138	0.86	0.34
<b>SKIN</b>	36	0.81	0.29

# Conclusion

- VOCs for human and rat data can be combined as shown on earlier slides.
- VOCs can be combined with drug data as shown before to give rise to predictive equations for small and large compounds in general.
- Equations to predict drug blood tissue distribution can be made for a number of tissues as shown before.

- **Professor Michael H Abraham**  
(project supervisor), **UCL, UK**
- **Professor William E Acree, UNT, USA**
- **UCL Team**
- **EPSRC funding studentship**



**THANK YOU.....**

**Presented by Adam Ibrahim**