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Original article

Air to fat and blood to fat distribution of volatile organic compounds and drugs: Linear free energy analyses

Michael H. Abraham*, Adam Ibrahim

Department of Chemistry, University College London, 20 Gordon Street, London, Middlesex WC1H OAJ, UK

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Abstract

Partition coefficients, K_{fat}, from air to human fat and to rat fat have been collected for 129 volatile organic compounds, VOCs. A linear free energy relationship, LFER, correlates the 129 values of log K_{fat} with $R^2 = 0.958$ and a standard deviation, S.D., of 0.194 log units. Use of training and test sets gives a predictive assessment of around 0.20 log units. Combination of log K_{fat} with our previously listed values of log K_{blood} enables blood/plasma to fat partition coefficients, as log P_{fat}, to be obtained for 126 VOCs. These values can be correlated with $R^2 = 0.847$, S.D. = 0.304 log units; the latter is also our assessment of the predictive capability of the LFER. Values of log P_{fat} have been collected for 46 drugs, and can be fitted to an LFER with $R^2 = 0.811$ and S.D. = 0.355 log units. Unlike partition into brain or muscle, the data for VOCs and drugs cannot be combined. There are marked discrepancies for PCBs for which partition from blood/plasma into fat is very much less than that calculated from the data on VOCs or from the data on drugs.

Keywords: Air–blood; Air–fat; Blood/plasma–fat; Volatile organic compounds; Drugs; PCBs; Linear free energy relationship

1. Introduction

Distribution of volatile organic compounds, VOCs, between air and tissues is of environmental and toxicological importance, and the distribution of organic compounds, both VOCs and drugs, between blood and tissues is of crucial importance in the understanding of potential toxic effects and in pharmacokinetic analysis. The importance of the air to fat tissue distribution of VOCs is shown by the considerable number of published papers [1–26] that list partition coefficients. These are measured at 37 °C and are defined through Eq. (1). If concentrations are expressed in the same units in air and fat, usually mol dm^{-1}, then the air to fat partition coefficient, K_{fat}, has no units, and is equivalent to the Ostwald solubility coefficient. These air to fat partition coefficients are obtained by an *in vitro* method in which the distribution of a compound between air and an isolated portion of fat is determined.

$$K_{fat}(in\ vitro) = \frac{\text{concentration of compound in fat}}{\text{concentration of compound in air}} \quad (1)$$

Although there is a reasonable quantity of data on K_{fat}(*in vitro*), only few attempts have been made to obtain correlative or predictive equations. Meulenberg and Vijverberg [1] found that values of K_{fat}(*in vitro*) could be described by a linear combination of air to olive oil and air to saline partition coefficients, K_{oil} and K_{saline}, as shown in Eqs. (2) and (3); note that different equations were constructed for human fat and rat fat.

$$K_{fat}(in\ vitro\ \text{human}) = 0.447K_{olive} + 0.075K_{saline} + 6.59 \quad (2)$$

$$N = 41,\ R^2 = 0.92,\ \text{S.D.} = \text{n/a},\ F = \text{n/a}$$

$$K_{fat}(in\ vitro\ \text{rat}) = 0.594K_{olive} + 0.085K_{saline} + 9.40 \quad (3)$$

$$N = 76,\ R^2 = 0.86,\ \text{S.D.} = \text{n/a},\ F = \text{n/a}$$

Here and elsewhere, N is the number of data points, usually the number of compounds, R is the correlation coefficient,

* Corresponding author. Tel.: +44 02076794639; fax: +44 02076797462.
E-mail address: m.h.abraham@ucl.ac.uk (M.H. Abraham).

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S.D. is the standard deviation, RMSE is the root mean square error and F is the F-statistic. Unfortunately, no S.D. values were given for Eqs. (2) and (3). Gargas et al. [3] showed that the air to rat fat partition coefficient was linearly related to the air to olive oil partition through Eq. (4), and that a double regression, Eq. (5), yielded similar statistics.

$$\log K_{\text{fat}}(\textit{in vitro}\ \text{rat}) = 0.920 \log K_{\text{olive}} + 0.136 \quad (4)$$

$$N = 55,\ R^2 = 0.946,\ \text{S.D.} = 0.187$$

$$\log K_{\text{fat}}(\textit{in vitro}\ \text{rat}) = 0.927 \log K_{\text{olive}} - 0.032 \log K_{\text{saline}} + 0.120 \quad (5)$$

$$N = 55,\ R^2 = 0.947,\ \text{S.D.} = 0.186$$

Abraham and Weathersby [4] studied air to human fat, and used the Abraham solvation equation to correlate the log K values; we shall consider this type of equation in detail, later.

$$\log K_{\text{fat}}(\textit{in vitro}\ \text{human}) = -0.294 - 0.172E + 0.729S + 1.747A + 0.219B + 0.895L \quad (6)$$

$$N = 36,\ R^2 = 0.988,\ \text{S.D.} = 0.118$$

The statistics, R^2 and S.D. for Eqs. (4)–(6) are quite impressive but refer only to fits and not to predictions.

A predictive assessment has been made by Katritzky et al. [27] who used literature data on air to both human blood and rat blood. For log K_{fat}(*in vitro* human) a four descriptor linear equation correlated 42 values with $R^2 = 0.918$, S.D. = 0.207 and $F = 104.1$, and a fragment based method with 18 fragments gave $R^2 = 0.974$, S.D. = 0.141 and $F = 53.4$. For rat fat, a five descriptor equation correlated 100 values with $R^2 = 0.906$, S.D. = 0.303 and $F = 180.9$, and a fragment method with 21 fragments correlated the 100 values with $R^2 = 0.939$, S.D. = 0.270 and $F = 60.4$. There were enough values to construct a training set and an independent test set. A training set of 66 compounds was fitted with 22 or 23 descriptors to give $R^2 = 0.973$ and S.D. = 0.161, and the equation was then used to predict log K_{fat}(*in vitro* rat) for 31 or 32 compounds with an S.D. of 0.230 log units. However, the latter was obtained from a plot of predicted against observed values, which is not correct − if the line does not go through the origin the obtained S.D. value will be too small.

Poulin and Krishnan [28] have presented a procedure to predict values of air to fat partition coefficients K_{fat}(*in vitro*) in rat, using data from Gargas et al. [3] and Kaneko et al. [26]. The required input values are the solubility in saline or water, the solubility in vegetable oil, and the saturated vapor pressure of the pure compounds. In this way, the average ratio between predicted and experimental values of K_{fat}(*in vitro*) was found to be 1.10; this corresponds to an S.D. of 0.13 log units (calculated in this work), which is quite impressive although only a very restricted data set was used. Note that Poulin and Krishnan [28] list the alcohol values of Kaneko et al. [26] as acetate esters, and the acetate ester values as alcohols, which must be a typographical error. More recently, Krishnan and co-workers [29] used a similar procedure to predict both K_{fat}(*in vitro*) in rat and in human, but this time calculated the required air to saline and air to vegetable oil partition coefficients by a fragmentation scheme. The average ratio between predicted and observed values of K_{fat}(*in vitro*) was 1.19 for rat fat and 1.20 for human fat; again, this refers to a very limited data set.

Once air to tissue partition coefficients are available, they can be combined with air to blood partition coefficients to obtain *in vitro* blood to tissue partition coefficients. Indeed, this is how the latter are usually obtained for VOCs. There have been a number of correlations of blood to fat distribution, P_{fat}(*in vitro*), reported. Abraham and Weathersby [4] used one of Abraham's LFERs to correlate values for 35 compounds through Eq. (6).

$$\log P_{\text{fat}}(\textit{in vitro}\ \text{human}) = 0.168 + 0.198E + 0.130S - 1.211A - 3.267B + 2.275V \quad (7)$$

$$N = 35,\ R^2 = 0.967,\ \text{S.D.} = 0.188$$

Balaz and Lukacova [30] used a rather complicated expression to correlate 36 values of log P_{fat}(*in vitro* human) with $R^2 = 0.960$ and S.D. = 0.20, and Zhang [31] also correlated 36 values using a nonlinear expression that yielded $R^2 = 0.972$ and S.D. = 0.178 log units.

To date, there has been no analysis that leads to any predictive assessment of equations for log P_{fat}(*in vitro*). It is our aim to obtain predictive equations for air to fat partition coefficients. We shall then use the database we have established for air to blood partitions to calculate blood to fat partition coefficients, and finally we shall attempt to obtain predictive equations for the latter partition coefficients.

2. Methods

Our method is based on the following two linear free energy relationships, LFERs:

$$\text{SP} = c + eE + sS + aA + bB + lL \quad (8)$$

$$\text{SP} = c + eE + sS + aA + bB + vV \quad (9)$$

In these equations [32,33], SP is the dependent variable. Eq. (8) is used to correlate air to tissue or air to solvent partitions, and SP is then log K_{blood} or log K_{fat}. Eq. (9) is used to correlate partition from one condensed phase to another, for example SP is then log P_{fat}. The dependent variables in Eqs. (8) and (9) are VOC properties, as we have recently discussed [34,35]. E is the solute excess molar refractivity in units of (dm^3 mol^{-1})/10, S is the solute dipolarity/polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, respectively, L is the logarithm of the gas–hexadecane partition coefficient at 25 °C, and V is the McGowan volume in units of (dm^3 mol^{-1})/100.

3. Results and discussion

3.1. Air to fat and blood to fat partition coefficients

Values of log K_{fat}(*in vitro*) that we have collected are in Table 1. These include values for some volatile inorganic gases, but we refer to the collection of compounds as VOCs. We give values for human fat and rat fat separately, and also averaged values. There are 30 compounds for which both partition into human fat and rat fat are available, and so it is possible to assess their similarity. Details are in Table 2, where we give the average error, AE, the absolute average error, AAE, and the standard deviation, S.D.; these statistics have been defined before [34,35]. The value of AE (rat−human) is so small as to be negligible, and so we can average the human fat and rat fat data. The values of AAE and S.D. are then an indication of random deviation, and indicate a rather small experimental error in log K_{fat}(*in vitro*) of 0.11 (AAE) or 0.14 (S.D.) log units.

The 129 averaged values of log K_{fat}(*in vitro*) listed in Table 1 were divided into a training set and a test set using the Kennard−Stone method [36] to ensure that the two sets covered the same region of chemical space. In this method, the descriptors for a given compound are chosen, and the data set is interrogated to find the compound with descriptors as near those of the first compound as possible. The two compounds are assigned to the training set and the test set, respectively. This process is continued until all the compounds have been assigned to one set or another. It is possible to select any proportion of compounds as the training set. We always chose the training and test sets to have equal number of compounds in order to facilitate the two sets occupying the same chemical space. We also constructed histograms for the descriptors of the training set and the test set to confirm that the Kennard−Stone method did, indeed, lead to similar distributions for the training set and the test set.

The 65 compounds in the training set yielded Eq. (10); the statistics include the cross-validated correlation coefficient, Q^2, which is a measure of self-consistency of the analysis. All the statistics so far, that is R^2, Q^2, S.D. and F, refer to goodness-of-fit. In order to assess goodness-of-prediction, the training equation, Eq. (10), can be used to predict the values of log K_{fat}(*in vitro*) for the remaining 64 compounds in the test set.

$$\log K_{fat}(in\ vitro) = -0.138 + 0.067E + 0.770S + 1.965A + 0.356B + 0.756L \quad (10)$$

$$N = 65,\ R^2 = 0.962,\ Q^2 = 0.951,\ \text{S.D.} = 0.217,\ F = 298.0$$

For the 64 test set compounds, analysis of the predicted and observed log K_{fat}(*in vitro*) values gave the goodness-of prediction statistics as an average error, AE = −0.036, an absolute average error, AAE = 0.142, an S.D. = 0.178, and an RMSE = 0.177 log unit. These statistics, together with those for Eq. (10) indicate that further values of log K_{fat}(*in vitro*) can be predicted to be about 0.15 (AAE) or 0.20 (SD) log units, with no bias in the predictions (AE = −0.036 only).

In order to obtain the most soundly based equation for log K_{fat}(*in vitro*), we can combine the training and test sets and obtain Eq. (11) for the full 129 compounds' data set.

$$\log K_{fat}(in\ vitro) = -0.052 + 0.051E + 0.728S + 1.783A + 0.332B + 0.743L \quad (11)$$

$$N = 129,\ R^2 = 0.958,\ Q^2 = 0.953,\ \text{S.D.} = 0.194,\ F = 562.8$$

There is very little cross-correlation of descriptors in Eq. (11), the maximum correlation being between E and S, with $R^2 = 0.25$ only. The fitting equations, Eqs. (10) and (11), compare very favorably with previous fitting equations [1,3,4,27–29], all of which have used fewer log K_{fat}(*in vitro*) values.

We have values of log K_{fat}(*in vitro*) for 129 VOCs, and can then combine them with values of log K_{blood}(*in vitro*) [34] to obtain corresponding log P_{fat} (*in vitro*) values, through Eq. (12).

$$\log P_{fat}(in\ vitro) = \log K_{fat}(in\ vitro) - \log K_{blood}(in\ vitro) \quad (12)$$

Both log K_{blood}(*in vitro*) and log P_{fat}(*in vitro*) are in Table 1. There are 126 values of log P_{fat}(*in vitro*) in Table 1, because we found that nonane, decane and 2-nitropropane were very considerable outliers to our equations for log P_{fat}(*in vitro*), by some 0.82 to 1.12 log units. We divide the 126 compounds into a training set of 63 and a test set of 63 using the Kennard−Stone method [36]. For the 63 VOCs in the training set, application of Eq. (9) yielded Eq. (13).

$$\log P_{fat}(in\ vitro) = 0.419 - 0.006E - 0.016S - 1.245A - 2.240B + 1.587V \quad (13)$$

$$N = 63,\ R^2 = 0.835,\ Q^2 = 0.812,\ \text{S.D.} = 0.311,\ F = 57.7$$

The fitting statistics of Eq. (13) are quite reasonable, and we can then use Eq. (13) to predict values of log P_{fat}(*in vitro*) for the 63 compounds in the test set. We find the prediction statistics: AE = −0.047, AAE = 0.249, S.D. = 0.305 and RMSE = 0.303 log units. Hence our method is capable of predicting log P_{fat}(*in vitro*) to about 0.30 (S.D.) or 0.25 (AAE) log units, with no bias in the predictions. We note that log K_{fat}(*in vitro*) is the average of human fat and rat fat, and that log K_{blood} values [34] are average values for human blood and rat blood. Hence Eq. (13) will apply to partition from human and rat blood to human and rat fat.

Finally, we can combine the training and test sets to obtain the more soundly based Eq. (14),

$$\log P_{fat}(in\ vitro) = 0.474 + 0.016E - 0.005S - 1.577A - 2.246B + 1.560V \quad (14)$$

$$N = 126,\ R^2 = 0.847,\ Q^2 = 0.827,\ \text{S.D.} = 0.304,\ F = 132.7$$

The fitting statistics and the coefficients of Eq. (14) are close to those of Eq. (13). These equations, Eqs. (13) and (14)

Table 1
Values of log K_{fat} for VOCs from air to human fat and air to rat fat, and values of log P_{fat} for VOCs from blood to fat

Solute	Human fat		Rat fat		Av fat		log P_{fat}
	log K_{fat}	Ref.	log K_{fat}	Ref.	log K_{fat}	log K_{blood}	
1,1,1,2-Tetrachloroethane			3.33	[1,3]	3.33	1.55	1.78
1,1,1-Trichloroethane	2.40	[2,4]	2.42	[1,3]	2.41	0.63	1.78
1,1,2,2-Tetrachloroethane			3.58	[1,3]	3.58	2.13	1.45
1,1,2-Trichloroethane			3.16	[1,3]	3.16	1.67	1.49
1,1-Dichloroethane			2.21	[1,3]	2.21	0.88	1.33
1,1-Dichloroethene			1.84	[1,3]	1.84	0.70	1.14
1,1-Dichloro-1-fluoroethane			1.56	[15]	1.56	0.32	1.24
1,2,4-Trimethylbenzene			3.25	[6,18]	3.25	1.47	1.78
1,2,4-Trimethylcyclohexane			3.19	[6,18]	3.19	0.87	2.32
1,2-Dibromoethane			3.09	[1,3]	3.09	2.08	1.01
1,2-Dichloroethane			2.54	[1,3]	2.54	1.39	1.15
1,2-Dichloropropane			2.7	[1,3]	2.70	1.14	1.56
1,2-Dimethylcyclohexane			3.24	[6]	3.24	0.91	2.33
1,3-Butadiene	1.35	[8]			1.35	0.09	1.26
1,2-Epoxy-3-butene			2.23	[24]	2.23	1.97	0.26
1-Bromo-2-chloroethane			2.98	[1,3]	2.98	1.60	1.38
1-Butanol			2.95	[1]	2.95	3.08	−0.13
1-Chloropropane			2.07	[1,3]	2.07	0.59	1.48
1-Nitropropane			2.7	[1,3]	2.70	2.31	0.39
1-Pentanol			3.41	[1]	3.41	2.83	0.58
1-Propanol	2.47	[1,2,4]	2.60	[1]	2.54	3.06	−0.52
1-Octene			2.89	[5]	2.89	1.07	1.82
1-Nonene			3.24	[5]	3.24	1.18	2.06
1-Decene			3.36	[5]	3.36	1.21	2.15
2,2,4-Trimethylpentane			2.47	[1,3]	2.47	0.23	2.24
2,2-Dimethylbutane	1.82	[1,2,4]			1.82	−0.59	2.41
2,2-Dichloro-1,1,1-trifluroethane			1.80	[16]	1.80	0.61	1.19
2,3,4-Trimethylpentane			2.65	[1,3]	2.65	0.57	2.08
2-Chloropropane			1.84	[1,3]	1.84	0.32	1.52
2-Heptanone			3.66	[1]	3.66	2.33	1.33
2-Methyl-1,3-butadiene			1.84	[1,3,17]	1.84	0.10	1.74
2-Methyl-1-propanol	2.59	[1,2,4]	2.86	[1]	2.73	2.92	−0.19
2-Methylpentane	1.94	[1,2,4]			1.94	−0.39	2.33
2-Methyl heptane			2.30	[5]	2.30	0.49	1.81
2-Methyl octane			2.56	[5]	2.56	0.52	2.04
2-Methyl nonane			2.84	[5]	2.84	0.76	2.08
2-Nitropropane			2.19	[1,3]	2.19		
2-Pentanone			2.57	[1]	2.57	2.14	0.43
2-Propanol	2.26	[1,2,4]	2.44	[1]	2.35	3.02	−0.67
3-Methyl-1-butanol			3.18	[1]	3.18	2.75	0.43
3-Methylhexane	2.44	[1,2,4]			2.44	0.11	2.33
3-Methylpentane	2.01	[1,2,4]			2.01	−0.37	2.38
4-Methyl-2-pentanone			2.72	[1]	2.72	1.96	0.76
4-Chlorobenzotrifluoride			2.99	[13]	2.99	1.43	1.56
Acetone	1.93	[1,2,4]	1.89	[1]	1.91	2.36	−0.45
Allyl chloride			2	[1,3]	2.00	1.24	0.76
Benzene	2.62	[1,2,4]	2.65	[1,3,6]	2.64	1.05	1.59
Bromochloromethane			2.51	[1,3]	2.51	1.21	1.30
Bromodichloromethane			2.72	[23]	2.72	1.49	1.23
Butan-2-one	2.21	[1,2,4]	2.30	[1]	2.26	2.24	0.02
Butyl acetate			3.18	[1]	3.18	1.94	1.24
Carbon tetrachloride			2.56	[1,3]	2.56	0.62	1.94
1-Chloro-2,2-difluroethene	1.30	[2,4]			1.30	0.06	1.24
Halothane	2.31	[1,2,4]	2.23	[1,3,16]	2.27	0.57	1.70
Teflurane	1.30	[1,4]			1.30	−0.22	1.52
1-Chloro-2,2,2-trifluroethane	1.53	[1,2,4]	1.33	[1,3]	1.43	0.14	1.29
Fluomar/fluroxene	1.53	[1,2,4]			1.53	0.15	1.38
Halopropane	2.35	[4]			2.35	0.75	1.60
Enflurane	1.97	[1,4]			1.97	0.35	1.62
Isoflurane	1.84	[1,2,4]	1.99	[1,3]	1.92	0.20	1.72
Sevoflurane	1.62	[1,2,4]			1.62	−0.20	1.82
Chlorobenzene			3.11	[1,3]	3.11	1.63	1.48

(continued on next page)

Table 1 (*continued*)

Solute	Human fat		Rat fat		Av fat		log P_{fat}
	log K_{fat}	Ref.	log K_{fat}	Ref.	log K_{fat}	log K_{blood}	
Chlorodibromomethane			3.28	[1,3]	3.28	1.88	1.40
Chloroethane			1.59	[1,3]	1.59	0.49	1.10
Chloroform	2.45	[1,2,4]	2.31	[1,3]	2.38	1.15	1.23
cis-1,2-Dichloroethene			2.36	[1,3]	2.36	1.16	1.20
Cyclohexane	2.41	[1,2,4]	2.47	[1,3,6]	2.44	0.17	2.27
Cyclopropane	0.99	[1,2,4]			0.99	−0.21	1.20
Cyanoethylene oxide			3.11	[7]	3.11	3.22	−0.11
Decane			3.05	[6]	3.05		
Dibromomethane			2.90	[1,3]	2.90	1.87	1.03
Dichloromethane	1.93	[1,2,4]	2.08	[1,3]	2.01	1.12	0.89
Diethyl ether	1.80	[1,2,4]	1.68	[1,3]	1.74	1.11	0.63
Difluromethane			0.16	[1,3]	0.16	0.20	−0.04
Divinyl ether	1.60	[1,2,4]			1.60	0.41	1.19
Ethanol	2.33	[1,2,4]	2.35	[1]	2.34	3.27	−0.93
Ethyl acetate			2.18	[1]	2.18	1.90	0.28
Ethyl *t*-butyl ether			2.13	[9]	2.13	1.07	1.06
2-Methyl-2-propanol			2.2	[9,25]	2.20	2.68	−0.48
Methyl *t*-butyl ether			1.97	[9,25]	1.97	1.18	0.79
Methyl *t*-amyl ether			2.52	[9]	2.52	1.22	1.30
2-Methyl-2-butanol			2.66	[9]	2.66	2.59	0.07
Ethylbenzene	3.25	[1]	3.19	[1]	3.22	1.47	1.75
Ethylene oxide	1.63	[21]	1.64	[20]	1.64	1.80	−0.17
Ethene	0.08	[1,4,21]	0.31	[21]	0.20	−0.53	0.73
Flurochloromethane			1.19	[1,3]	1.19	0.71	0.48
Furan			1.81	[11]	1.81	0.82	0.99
Heptane	2.59	[1,2,4]	2.42	[1,3,6]	2.51	0.50	2.01
Hexachloroethane			3.52	[1,3]	3.52	1.76	1.76
Hexane	2.02	[1,2,4]	2.22	[1,3,6]	2.12	0.21	1.91
Isobutyl acetate			3.05	[1]	3.05	1.69	1.36
Isopentyl acetate			3.44	[1]	3.44	1.79	1.65
Isopropyl acetate			2.48	[1]	2.48	1.55	0.93
2-Bromopropane			2.2	[1,3]	2.20	0.64	1.56
JP-10			4.01	[3]	4.01	1.76	2.25
Krypton	−0.48	[4]			−0.48	−1.22	0.74
Methoxyflurane	2.90	[1,2,4]			2.90	1.28	1.62
Methanol	2.36	[1,2]	2.29	[1]	2.33	3.41	−1.08
Methyl acetate			2	[1]	2.00	1.98	0.02
Chloromethane			1.13	[1,3]	1.13	0.31	0.82
Methylcyclopentane	2.25	[1,2,4]			2.25	−0.07	2.32
Methylcyclohexane			2.65	[6]	2.65	0.70	1.95
m-Methylstyrene			4.08	[1,3]	4.08	2.28	1.80
m-Xylene	3.28	[1]	3.30	[1,3]	3.29	1.59	1.70
Nitrogen	−1.27	[4]			−1.27	−1.83	0.56
Nitrous oxide	0.04	[2,4]			0.04	−0.34	0.38
Nonane			2.92	[6,18]	2.92		
Octane	2.71	[1,4]	2.73	[6]	2.72	0.68	2.04
o-Xylene	3.39	[1]	3.00	[1,3,6]	3.20	1.42	1.78
Pentachloroethane			3.61	[1,3]	3.61	2.02	1.59
Pentane	1.60	[1,2,4]			1.60	−0.29	1.89
Pentyl acetate			3.57	[1]	3.57	1.98	1.59
p-Methylstyrene			4.05	[1,3]	4.05	2.37	1.68
Propyl acetate			2.71	[1]	2.71	1.88	0.83
1-Bromopropane			2.37	[1,3]	2.37	0.97	1.40
Propene	0.71	[10]	0.80	[10]	0.76	−0.21	0.97
p-Xylene	3.31	[1]	3.24	[1,3]	3.28	1.61	1.67
Radon			0.68	[12]	0.68	−0.39	1.07
Styrene	3.50	[1]	3.54	[1,3]	3.52	1.67	1.85
t-Butylcyclohexane			3.17	[6]	3.17	1.16	2.01
t-Butylbenzene			3.26	[6]	3.26	1.24	2.02
Tetrachloroethene			3.21	[1,3]	3.21	1.19	2.02
Toluene	2.95	[1,2,4]	2.89	[1,3,6]	2.92	1.14	1.78

Table 1 (*continued*)

Solute	Human fat		Rat fat		Av fat		log P_{fat}
	log K_{fat}	Ref.	log K_{fat}	Ref.	log K_{fat}	log K_{blood}	
trans-1,2-Dichloroethene			2.17	[1,3]	2.17	0.88	1.29
Trichloroethene	2.77	[1,2,4]	2.72	[1,3,19]	2.75	1.14	1.61
Vinyl bromide			1.69	[1,3]	1.69	0.49	1.20
Vinyl chloride	1.30	[22]	1.30	[1,3,22]	1.30	0.17	1.13
1,1-Difluoroethene			−0.10	[14]	−0.10	−0.74	0.64
Xenon	0.26	[2]			0.26	−0.85	1.11

appear to be the only equations available for the prediction of blood to fat partition coefficients.

In addition to the indirect values of log P_{fat}(*in vitro*), there are also available direct *in vivo* values for a number of drugs, determined by administering the drug to rats, followed by the determination of the steady state drug concentrations in blood or plasma and in fat [37–48]. Values are collected in Table 3 for 46 drugs. Application of Eq. (9) yields Eq. (15); we have included a few drugs twice, because the log P values have been determined separately, and we have excluded biperiden that is a considerable outlier. Thus N in Eq. (15) refers to the number of data points.

$$\log P_{fat}(in\ vivo) = 0.077 + 0.249E - 0.215S - 0.902A - 1.523B + 1.234V - 1.013\mathrm{Ia} \quad (15)$$

$$N = 50,\ R^2 = 0.811,\ Q^2 = 0.742,\ \mathrm{S.D.} = 0.355,\ F = 30.7$$

For partition of carboxylic acids from blood to brain [35,49–51], an indicator variable was needed to bring them into line; Ia takes the value zero except for carboxylic acids when Ia = 1. We used this indicator variable in Eq. (15), and found it to be significant at the 99.9% level. Unlike our previous analysis of *in vitro* and *in vivo* partition of VOCs and drugs from blood to brain and blood to muscle, the coefficients in the *in vitro* and *in vivo* equations for partition from blood to fat are substantially different. If we combine the data for VOCs and drugs, the resulting equation will have coefficient values somewhere between those in Eqs. (14) and (15), as given in Eq. (16).

$$\log P_{fat}(in\ vivo + in\ vitro) = 0.122 + 0.158E - 0.142S - 1.057A - 1.950B + 1.521V - 1.037\mathrm{Ia} + 0.321\mathrm{Iv} \quad (16)$$

Table 2
Analysis of log K_{fat} values for air to human fat and air to rat fat

Statistic	Value
N	30
AE	0.009
AAE	0.105
S.D.	0.140

$$N = 176,\ R^2 = 0.869,\ Q^2 = 0.853,\ \mathrm{S.D.} = 0.330,\ F = 159.2$$

In Eq. (15) we have used the Iv indicator variable that we showed was useful when we combined data for VOCs and drugs for partition from blood to brain (49). Iv takes the value zero for *in vivo* determinations of drugs and 1 for *in vitro* determination of VOCs, and is significant at the 99.7% level in Eq. (16).

A plot of calculated against observed values of log P_{fat}(*in vivo* + *in vitro*) for VOCs and drugs based on Eq. (16) is shown in Fig. 1. It is clear that the values for drugs and VOCs do not lie on the same line. This result is quite different from partition from blood into brain, where the VOCs and drugs can be fitted quite well to the same equation [49], and suggests that there is some particular additional interaction in fat.

In addition to the *in vivo* values for drugs, there are also available log P_{fat}(*in vivo*) values for polychlorobiphenyls, PCBs, as shown in Table 3 [52–55]. We have not included values for any of the PCBs in Eq. (16), but the predicted and observed values of log P_{fat} are also shown in Fig. 1. There are even larger discrepancies than for the drugs, and the observed values for the PCBs are always much smaller than predicted. The hydrophobic compound *p*,*p*′-DDE behaves similarly to the PCBs. We suggest that Eq. (14) be used to predict further values of partition into fat for VOCs and that (the less satisfactory) Eq. (15) be used to estimate values for drugs. Parham et al. [56] have used the data of Wolff et al. [55] to predict partition from human plasma to fat for the remaining PCBs, and this method of predicting PCB values just from data on PCBs seems to be the best available.

We can obtain further information on the PCBs, which are hydrophobic compounds, by comparing them with other hydrophobic compounds in Table 3. None of the drugs can be considered hydrophobic, but many of the VOCs are. Now for hydrophobic compounds, that by definition will have small values of S, A, and B, a plot of log P values in one partition system against log P values in another system will yield an approximate straight line. Values of the water to octanol partition coefficient, as log P(oct), are available for most of the hydrophobic VOCs and for some of the PCBs, and a plot of log P(oct) against observed values of log P_{fat}(*in vivo* + *in vitro*) is shown in Fig. 2. The observed values for the PCBs, and the value for *p*,*p*′-DDE, are much smaller than expected, exactly as indicated

Table 3
Blood/plasma to fat partition coefficients for drugs and polychlorobiphenyls, as log P_{fat}

Solute	log P_{fat}	Medium	Ref.
Biperiden	1.76	Rat plasma	[37]
Cocaine	0.83	Rat plasma	[38]
Daidzein	−0.54	Rat blood	[39]
Hexobarbital	0.20	Rat plasma	[37]
Midazolam	0.94	Rat blood/plasma	[37,40]
Nalidixic acid	−1.00	Rat plasma	[37]
Pentazocine	0.40	Rat plasma	[37]
Phenobarbital	−0.52	Rat plasma	[37]
Phenytoin	0.26	Rat plasma	[37]
Procainamide	−0.89	Rat plasma	[37]
R-Etodolac	−1.17	Rat plasma	[37]
S-Etodolac	−0.77	Rat plasma	[37]
Thiopental (Thiopentone)	0.89	Rat plasma	[37]
Valproic acid	−0.82	Rat plasma	[37]
Methohexital	0.60	Human plasma	[41]
Thiopental	0.95	Human plasma	[41]
Imipramine	1.02	Rat plasma	[41]
Nicotine	−0.46	Rat plasma	[41]
Pentazocine	0.40	Rat plasma	[41]
5-Ethyl-5-(1-methylbutyl)barbital	0.11	Rat plasma	[41]
Phenobarbital	−0.49	Rat plasma	[41]
Phenytoin	0.18	Rat plasma	[41]
Procaine	−0.35	Rat plasma	[41]
Thiobarbital	−0.05	Rat plasma	[41]
Thiopental	0.81	Rat plasma	[41]
AI-1 (CDRI-81/470)	−0.96	Rat serum	[42]
Terbinafine	1.60	Rat plasma	[43]
Diazepam	1.13	Rat plasma	[44]
o-Ethoxybenzamide	−0.17	Rat plasma	[44]
Midazolam	0.95	Human plasma	[45]
5-Methyl-5-ethyl barbituric acid	−0.46	Rat plasma	[46]
5-Propyl-5-ethyl barbituric acid	0.12	Rat plasma	[46]
5-Butyl-5-ethyl barbituric acid	0.25	Rat plasma	[46]
5-Pentyl-5-ethyl barbituric acid	0.54	Rat plasma	[46]
5-Hexyl-5-ethyl barbituric acid	1.08[a]	Rat plasma	[46]
5-Heptyl-5-ethyl barbituric acid	0.94[a]	Rat plasma	[46]
5-Octyl-5-ethyl barbituric acid	0.66[a]	Rat plasma	[46]
5-Nonyl-5-ethyl barbituric acid	0.69[a]	Rat Plasma	[46]
5,5-Diethyl barbituric acid	−0.14	Rat plasma	[46]
p,p′-Dichlorodiphenylsulfone	2.03	Rat blood	[47]
Acebutolol	−0.03	Rat plasma	[48]
Betaxolol	0.46	Rat plasma	[48]
Biperiden	1.90	Rat plasma	[48]
Bisoprolol	0.01	Rat plasma	[48]
Fentanyl	1.43	Rat plasma	[48]
Imipramine	1.02	Rat plasma	[48]
Inaperisone	1.19	Rat plasma	[48]
Metoprolol	0.01	Rat plasma	[48]
Nicotine	−0.30	Rat plasma	[48]
Oxprenolol	−0.20	Rat plasma	[48]
Pentazocine	0.39	Rat plasma	[48]
Phencyclidine	1.79	Rat plasma	[48]
Pindolol	−0.06	Rat plasma	[48]
Procainamide	−0.89	Rat plasma	[48]
Propranolol	0.19	Rat plasma	[48]
Timolol	−0.19	Rat plasma	[48]
4-Chlorobiphenyl	1.48	Rat blood	[52]
4,4′-Dichlorobiphenyl	1.85	Rat blood	[52]
2,2′,4,5,5′-Pentachlorobiphenyl	1.85	Rat blood	[52]
2,2′,4,4′,5,5′-Hexachlorobiphenyl	2.60	Rat blood	[52]
3,3′,5,5′-Tetrachlorobiphenyl	2.34	Rat blood	[53]
2,2′,3,3′,5,5′-Hexachlorobiphenyl	2.01	Rat blood	[54]
2,2′,3,3′,6,6′-Hexachlorobiphenyl	1.95	Rat blood	[54]
2,2′,4,4′,5,5′-Hexachlorobiphenyl	2.06	Rat blood	[54]
2,2′,4,4′,6,6′-Hexachlorobiphenyl	1.95	Rat blood	[54]
4,4′-Dichlorobiphenyl	1.95	Human plasma	[55]
2,4,4′-Trichlorobiphenyl	2.30	Human plasma	[55]
2,2′,5,5′-Tetrachlorobiphenyl	1.90	Human plasma	[55]
2,2′,4,5-Tetrachlorobiphenyl	1.95	Human plasma	[55]
2,2′,4,4′-Tetrachlorobiphenyl	2.49	Human plasma	[55]
2,2′,3,5′-Tetrachlorobiphenyl	1.90	Human plasma	[55]
2,4,4′,5- Tetrachlorobiphenyl	2.30	Human plasma	[55]
2,3′,4,4′-Tetrachlorobiphenyl	2.20	Human plasma	[55]
2,3′,4′,5-Tetrachlorobiphenyl	1.85	Human plasma	[55]
2,2′,3,5′,6-Pentachlorobiphenyl	1.78	Human plasma	[55]
2,2′,4,5,5′-Pentachlorobiphenyl	1.70	Human plasma	[55]
2,2′,4,4′,5-Pentachlorobiphenyl	2.38	Human plasma	[55]
2,3,3′,4,4′-Pentachlorobiphenyl	2.11	Human plasma	[55]
2,3′,4,4′,5-Pentachlorobiphenyl	2.25	Human plasma	[55]
2,2′,3,4′,5,5′-Hexachlorobiphenyl	2.48	Human plasma	[55]
2,2′,4,4′,5,5′-Hexachlorobiphenyl	2.43	Human plasma	[55]
2,3,3′,4,5,5′-Hexachlorobiphenyl	2.56	Human plasma	[55]
2,3,3′,4,4′,5-Hexachlorobiphenyl	2.49	Human plasma	[55]
2,3′,4,4′,5,5′-Hexachlorobiphenyl	2.08	Human plasma	[55]
2,2′,3,4,4′,5′-Hexachlorobiphenyl	2.04	Human plasma	[55]
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl	2.56	Human plasma	[55]
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl	2.43	Human plasma	[55]
2,2′,3,4′,5,5′,6-Heptachlorobiphenyl	2.57	Human plasma	[55]
2,2′,3,4,4′,5′6-Heptachlorobiphenyl	2.20	Human plasma	[55]
2,2′,3,3′,4′,5,5′,6-Octachlorobiphenyl	2.42	Human plasma	[55]
p,p′-DDE	2.23	Human plasma	[55]

[a] Not used in any regressions, see Ref. [46].

in Fig. 1. Note that no drugs are shown in Fig. 2 because none of them can be classed as hydrophobic. The peculiar nature of the PCBs as shown in Fig. 1 is not an artifact due to incorrect descriptors or an inadequate correlation equation, but seems to be an inherent property of the PCBs. This is an important finding, because hydrophobic environmental contaminants tend to accumulate in fat (adipose tissue) in humans and animals.

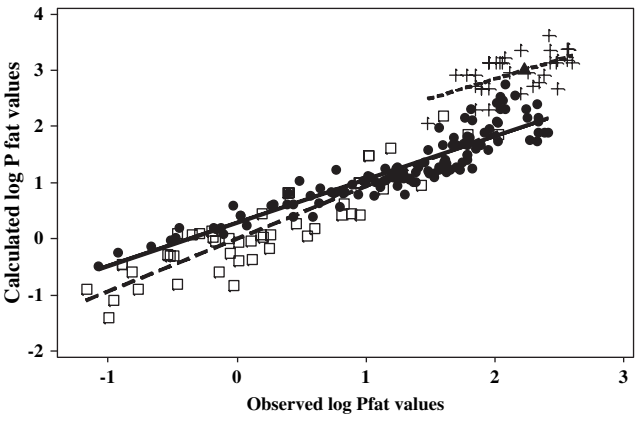

Fig. 1. A plot of calculated against observed values of log P_{fat}. Calculated values based on Eq. (15): ● VOCs, □ drugs, + PCBs, ▲ *p,p′*-DDE. The full line is that calculated for VOCs only, and the dashed lines are those calculated for drugs and PCBs.

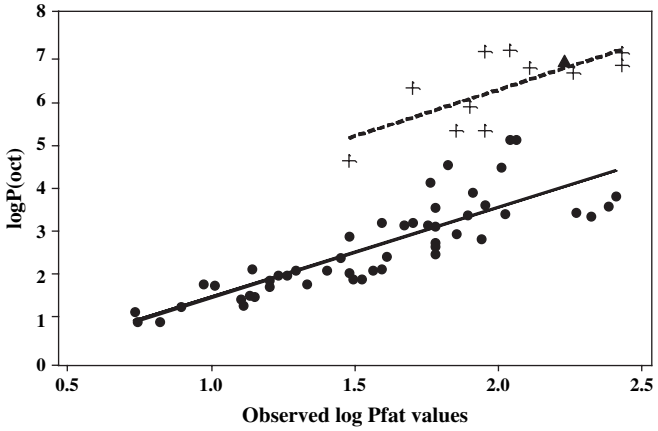

Fig. 2. A plot of log P(oct) against observed values of log P_{fat} for hydrophobic compounds: ● VOCs, + PCBs, ▲ p,p'-DDE.

The descriptors we have used have previously been published for VOCs and drugs [33–35,49] and the PCBs [57]. Descriptors for other VOCs or drugs are listed [59] and can also be calculated by the method of Platts et al. [58], or the method of PharmaAlgorithms [59], so that the various partition coefficients can be obtained for other VOCs and drugs.

3.2. The coefficients in the LFERs

As we have previously suggested, the coefficients in the LFERs, Eqs. (8) and (9), are not just fitting coefficients, but contain information on the chemical properties of the phases involved. Since Eq. (8) refers to the difference between properties of the gas phase and the condensed phase, it is easier to interpret than Eq. (9) which refers to the difference in properties of two condensed phases. Values of the coefficients in Eq. (8) for a number of processes are shown in Table 4; these include air to muscle, for which we have recently obtained the coefficients in Eq. (8) [60]. Fat resembles lipid-like solvents such as olive oil much more than the phases brain, muscle and blood resemble lipid-like solvents. This is exactly as expected from the high lipid content of fat. Indeed, except that the fat equation has a small b-coefficient, there is a marked resemblance to the olive oil equation. The b-coefficients imply that fat has some hydrogen bond acidity, whereas olive oil does not have any hydrogen bond acidity. In general, the coefficients for the fat equation are consistent with a phase that is quite lipophilic, but with considerable hydrogen bond basicity and some hydrogen bond acidity.

4. Conclusions

We have obtained a new equation for log K_{fat}(*in vitro*) based on data for 129 compounds. The only previous method that uses anywhere near this number of compounds is that of Katritzky et al. [27] who fitted 100 compounds with $R^2 = 0.906$ and S.D. = 0.303 as compared to our fit with $R^2 = 0.958$ and S.D. = 0.194, as in Eq. (11). The prediction goodness-of-fit in the procedure of Katritzky et al. [27] is quite good, with S.D. = 0.23 for 32 compounds, as compared to our predicted goodness-of-fit which is S.D. = 0.18 log units for 64 compounds.

A decided advantage of the present method is that it is possible to compare equations for different processes, and to obtain information as to the various chemical interactions that dominate the processes. Thus inspection of Table 4 shows that air to brain or air to muscle equations are dominated by large a- and b-coefficients, and hence compounds that are strong hydrogen bond acids and strong hydrogen bond bases will readily partition into brain and muscle. In the case of air to fat partition, interactions involving hydrogen bond acids and especially hydrogen bond bases are much weaker, and the 'size' or 'nonpolar' term lL becomes more significant.

Although our analysis of blood to fat partition appears to be less successful than that of air to fat, it is still very informative. In particular, we show that important hydrophobic compounds such as the PCBs and p,p'-DDE partition from blood to fat very much less than expected from data on VOCs.

All the calculations and regressions were carried out using Minitab, version 14 [61]. The descriptors used in the various equations are available as an Excel spreadsheet from the authors.

Table 4
Coefficients in the LFER, Eq. (8), for air to various phases at 25 °C or 37 °C

Solvent	c	e	s	a	b	l
Water, 25	−1.271	0.822	2.743	3.904	4.814	−0.213
Blood, 37	−1.069	0.456	1.083	3.738	2.580	0.376
Muscle, 37	−1.039	0.207	0.723	3.242	2.469	0.463
Brain, 37	−0.987	0.263	0.411	3.358	2.025	0.591
Fat, 37, Eq. (11)	−0.052	0.051	0.728	1.783	0.332	0.743
Octan-1-ol (dry), 25	−0.120	−0.203	0.560	2.560	0.702	0.939
N-Methylformamide, 25	−0.599	−0.259	2.003	4.559	0.430	0.706
Olive oil, 37	−0.230	0.009	0.795	1.353	0.000	0.888
Plant cuticle, 25	−0.617	0.082	1.282	3.120	0.820	0.860

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