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Original article

Air to brain, blood to brain and plasma to brain distribution of volatile organic compounds: linear free energy analyses

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Abstract

Partition coefficients, K_{brain}, for volatile organic compounds, VOCs, from air to brain have been collected for 81 compounds (air to human brain and air to rat brain). For the 81 VOCs a linear free energy equation (LFER) correlates log K_{brain} with $R^2 = 0.923$ and S.D. = 0.346 log units. Use of training and test sets gives a predictive assessment of 0.35–0.40 log units. Combination of log K_{brain} with our previously listed values of log K_{blood} enables blood to brain partition, as log $P_{b\text{-}brain}$, to be obtained for 78 VOCs. These values can be correlated with $R^2 = 0.725$ and S.D. = 0.203 log units; use of training and test sets allows a predictive assessment for log $P_{b\text{-}brain}$ of 0.16–0.20 log units. Values for air to plasma were available for 21 VOCs. When these data were combined with the data on air to blood and air to brain, values for partition between (blood or plasma) to brain, $P_{bp\text{-}brain}$, were available for 99 VOCs. A LFER correlates this data with $R^2 = 0.703$ and S.D. = 0.197 log units; use of training and test sets allows a predictive assessment for log $P_{bp\text{-}brain}$ of 0.15–0.20 log units.

Keywords: Air–blood; Air–brain; Blood–brain; Plasma–brain; Volatile organic compounds; Linear free energy relationship

1. Introduction

The distribution of organic compounds between blood and tissues is of crucial importance in the understanding of potential toxic effects. For volatile organic compounds, VOCs, the usual method of determination of blood to tissue partition coefficients is separately to obtain the corresponding air to blood and air to tissue partition coefficients. The importance of the subject is illustrated by the very large number of published investigations, especially of blood to brain partition. We have previously [1] studied the air to blood partition coefficients of VOCs, with respect to human blood, log K_{blood} (human), and to rat blood, log K_{blood} (rat). Note that in these studies [1] and in the present work, the set of compounds includes a number of inorganic gases. However, we shall use the term VOCs to cover both volatile inorganic and volatile organic compounds. The defining equation for air to blood partition, at 37 °C, is:

$$K_{blood} = [\text{conc. of compound in blood}]/[\text{conc. of compound in air}] \quad (1)$$

Concentrations of VOCs are expressed as mol dm^{-1} in blood and in air, so that K_{blood} has no units, and is equivalent to the Ostwald solubility coefficient.

It has been suggested that K_{blood} (human), and K_{blood} (rat) are not quite the same, and ratios of K_{blood} (rat)/K_{blood} (human) of 1.5–2.0 have been observed [2]. Other workers [3] found ratios between 1.3 and 1.7 and ratios as low as 1.08 for esters have been observed [4]. We have found previously [1] that for 86 common VOCs the average error, AE, between the two sets of log K_{blood} values is only 0.12 log units, corresponding to a ratio of 1.3 and smaller than our estimated experimental error between laboratories. We therefore suggested [1] that values of

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log K_{blood} (human), and log K_{blood} (rat) could be taken together in order to obtain relationships that could be used to predict further values of log K_{blood}.

We were able to collect values of log K_{blood} (human) for 155 VOCs and of log K_{blood} (rat) for 127 VOCs, giving values for a total of 196 individual VOCs. The aims of the present work are to collect data on log K_{brain} for VOCs, to devise a predictive equation for log K_{brain}, and then to combine the two sets of data for log K_{blood} and log K_{brain} to yield values for partition from blood to brain, log $P_{b\text{-}brain}$, and finally to obtain a predictive equation for log $P_{b\text{-}brain}$. We note at the outset, that values of log K_{brain} or log $P_{b\text{-}brain}$ obtained from some particular equation are often referred to as 'predicted values'. We shall refer to these only as 'calculated values' and reserve the term 'predicted values' for true predictions obtained from an independent set of values, the 'test set', that has not been used to construct a particular equation.

Although there has been much interest in air to brain partition of VOCs, there have been few correlations of log K_{brain} reported. An early attempt used a correlation against air to water and air to oil partitions, but only for 17 compounds [5]. A version of the methodology used in the present paper was applied to 41 compounds [6] and a double regression method was used to correlate values of log K_{brain} for 35 VOCs [3]. Details of the latter two analyses are presented in Table 1. No independent test sets of compounds were used, and so the predictive capability of the equations is unknown. The average error is denoted as AE, the absolute average error as AAE, and the standard deviation as S.D. In addition to these correlations, Krishnan and co-workers (Beliveau et al. [7,8]) have set out a physiologically based method for air to tissue partition coefficients, based on partition coefficients for air to water, air to vegetable oil and air to protein, the latter, in turn, being estimated by a fragmentation method. They studied 48 VOCs that formed a restricted chemical set of hydrocarbons and halogenated hydrocarbons. Since air to brain partitions were not considered, we can make no comparison with our results.

The situation with respect to the correlation and prediction of blood to brain partition coefficients, as log $P_{b\text{-}brain}$, for VOCs is almost as unsatisfactory. A connection between blood to brain and blood to fat partitions has been noted for 35 VOCs [9], but this is not very useful as a predictive method. A version of the present method was used to correlate log $P_{b\text{-}brain}$ for 39 VOCs [6], and a rather complicated expression involving water to octanol partition coefficients, P_{oct}, was applied to 35 VOCs [10]. Various descriptors have been used in a nonlinear expression to correlate values of log $P_{b\text{-}brain}$ for 35 VOCs [11]. In none of these cases was any test set used, and so the predictive capability of the equations cannot be assessed. Details are presented in Table 2.

Table 1
Statistics for the correlation and prediction of log K_{brain} for VOCs from Eqs. (4), (5) and (6). Comparison with previous work

		Training set			Test set			
Reference	[a]	N	R^2	S.D.	N	S.D.	AAE	AE
[6]	H	41	0.97	0.24				
[3]	H	35	0.98					
[3]	R	19	0.90					
Eq. (4) [d]	HR	41	0.93	0.34	40	0.41	0.35	–0.14
Eq. (5) [d]	HR	40	0.93	0.33	41	0.42	0.31	0.08
Eq. (6) [d]	HR	81	0.92	0.35				

[a] H human blood, R rat blood.
[d] This work. HR indicates human and rat data averaged. N is the number of data points, R is the correlation coefficient, S.D. is the standard deviation, AAE is the average absolute error, and AE is the average error.

Table 2
Statistics for the correlation and prediction of log $P_{b\text{-}brain}$ for VOCs from Eqs. (7), (8), (9), (13) and (14). Comparison with previous work

		Training set			Test set			
Reference	[a]	N	R^2	S.D.	N	S.D.	AAE	AE
[6]	H	39	0.87	0.15				
[10]	H	35	0.96	0.08				
[11]	H	35	0.92	0.12				
Eq. (7) [e]	HR	39	0.66	0.22	39	0.20	0.15	0.03
Eq. (8) [e]	HR	39	0.78	0.20	39	0.21	0.16	0.02
Eq. (9) [e]	HR	78	0.72	0.20				
Eq. (13) [f]	HR	50	0.70	0.21	49	0.20	0.15	0.00
Eq. (14) [f]	HR	99	0.69	0.20				

[a] H human blood, R rat blood.
[e] This work. HR indicates human and rat data averaged.
[f] This work, for partition from blood or plasma to brain. N is the number of data points, R is the correlation coefficient, S.D. is the standard deviation, AAE is the average absolute error, and AE is the average error.

2. Methods

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

$$SP = c + e.E + s.S + a.A + b.B + l.L \quad (2)$$

$$SP = c + e.E + s.S + a.A + b.B + v.V \quad (3)$$

In these equations, SP is the dependent variable. Eq. (2) is used to correlate air to tissue or air to solvent partitions, and SP is then log K_{blood} or log K_{brain}. Eq. (3) is used to correlate partition from one condensed phase to another, for example SP is then log $P_{b\text{-}brain}$. The dependent variables in Eqs. (2) and (3) are VOC properties, as discussed several times [12,13]. **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, **L** is the logarithm of the gas-hexadecane partition coefficient at 25 °C, and **V** is the McGowan volume in units of $(dm^3\ mol^{-1})/100$. We chose to use Eqs. (2) and (3) because these are well-known general equations that have been used many times to correlate gas to solvent and water to solvent partition coefficients [12–14], Furthermore, the descriptors in Eqs. (2) and (3) are available for some 3000 compounds, and can be predicted just from structure, if required [14], so that application of Eqs. (2) and (3) to the prediction of further values of the dependent variables is extremely easy and straightforward.

3. Results and discussion

3.1. Air to brain partition coefficients

Values of log K_{brain} that we have assembled for VOCs are collected in Table 3, where we distinguish those obtained for human brain and rat brain. There are 17 overlapping data points and so we can investigate any possible difference. The simplest, and statistically the best, method is to compare the two sets of data, log K_{brain} (human) and log K_{brain} (rat). Then $\sum[\log K_{brain}(\text{rat}) - \log K_{brain}(\text{human})]/N$, where N is the number of values (17 in the present case) is the average difference between the two sets of measurements. This is known as the average error, AE. The larger is AE numerically, the more the two sets diverge in a systematic manner. Results are in Table 4, where AE is given as 0.062 log units. This is very small indeed, and shows that within any realistic experimental error, the two sets of measurement are statistically the same. We have therefore combined the two sets, as in Table 3. The other statistics are measures of random deviations in log K_{brain} (rat) and log K_{brain} (human), and are defined as follows. The average absolute error, AAE, is given by the absolute values of [log K_{brain} (rat) – log K_{brain} (human)] divided by N. The standard deviation, S.D., is defined as $\sqrt{\sum\{[\log K_{brain}(\text{rat}) - \log K_{brain}(\text{human})]^2/(N-1)\}}$, and the root mean square error, RMSE, is defined as $\sqrt{\sum\{[\log K_{brain}(\text{rat}) - \log K_{brain}(\text{human})]^2/(N)\}}$. Although AAE, S.D. and RMSE are all used as a measure of random deviations, S.D. and RMSE are the more realistic measures and suggest that the experimental error in the log K_{brain} data must be around 0.25 log units, that is considerably higher than the AE of only 0.062 log units.

In Table 3, are the values of log K_{brain} for 81 VOCs [3,6,9,15–25], with an average value given for human brain and rat brain. This represents the largest set of data on log K_{brain} yet published and should be of value to other workers in the field. There are enough data to construct a training set (A) of 41 VOCs and an independent test set (B) of 40 VOCs, chosen by the Kennard and Stone method [26]. The training set yielded Eq. (4):

$$\text{Log}K_{brain}(\text{set A}) = -1.018 + 0.560E + 0.563S + 3.440A + 2.240B + 0.521L \quad (4)$$

$N = 41$, $R^2 = 0.930$, S.D. = 0.342, RMSE = 0.317, $F = 92.7$

Here and elsewhere, N is the number of data points, R is the correlation coefficient, S.D. is the standard deviation and RMSE is the root mean square error. Note that in a multiple linear regression equation, the denominator in the definition of S.D. is N – P – 1 and in the definition of RMSE it is N – P, where P is the number of independent variables in the equation.

This training set (A) was then used to predict log K_{brain} for the independent test set (B). For the predictions we find $N = 40$, AE = –0.136, AAE = 0.347, S.D. = 0.409 and RMSE = 0.404. We can also use the sets in reverse, and take set (B) as the training set, when we obtain Eq. (5):

$$\text{Log}K_{brain}(\text{set B}) = -0.966 - 0.357E + 0.661S + 3.565A + 1.604B + 0.636L \quad (5)$$

$N = 40$, $R^2 = 0.933$, S.D. = 0.331, RMSE = 0.307, $F = 95.4$

Then Eq. (4) can be used to predict the test set (A) for which we find $N = 41$, AE = 0.076, AAE = 0.315, S.D. = 0.418 and RMSE = 0.413

Finally, we can combine the training set and the test set, and obtain Eq. (6):

$$\text{Log}K_{brain} = -0.987 + 0.263E + 0.411S + 3.358A + 2.025B + 0.591L \quad (6)$$

$N = 81$, $R^2 = 0.923$, S.D. = 0.346, RMSE = 0.333, $F = 179.0$

In setting up the training sets and test sets, we left out methanol and cyanoethylene oxide. In both cases, the experimental and calculated values differed by over one log unit. We have no explanation for this, other than possible experimental error. A comparison of our results with those of previous workers [3,6] is in Table 1. The various training, or fitting, equations are comparable. Our assessment of the predictive capability of Eqs. (4) and (5) and, by implication, of Eq. (6) suggests that further values of log K_{brain} could be predicted to about 0.35 log units. This is not far from the random experimental error that we suggest is near 0.2–0.3 log units; note that the experimental error on log K_{blood} was found to be around 0.2 log units [1].

3.2. Blood to brain partition coefficients

Now that we have values of log K_{brain} for 81 VOCs, we can combine them with corresponding values of log K_{blood} [1]; both sets of data refer to average values for human and rat. The obtained values for partition of VOCs between blood and brain, as log $P_{b\text{-}brain}$, are collected in Table 5. There are 78 VOCs for which we can obtain log $P_{b\text{-}brain}$ values. As usual, we split them into a training set (A) and an independent test set (B). For the training set of 39 compounds we find,

$$\text{Log}P_{b-brain}(\text{set A}) = 0.009 + 0.053E - 0.584S - 0.238A - 0.338B + 0.638V \quad (7)$$

$N = 39$, $R^2 = 0.657$, S.D. = 0.215, RMSE = 0.198, $F = 12.7$

The correlation coefficient in Eq. (7) is disappointing, but there is a quite small S.D. value. From Eq. (7) we can predict values of log $P_{b\text{-}brain}$ for the independent test set (B) of 39 VOCs. We find almost no bias in the predictions, with AE = –0.027 only, and good predictive capability as shown by AAE = 0.155, S.D. = 0.203 and RMSE = 0.200 log units. Again we can reverse the sets, and for the training set (B) we find,

$$\text{Log}P_{b-brain}(\text{set B}) = -0.119 - 0.002E - 0.469S - 0.372A - 0.360B + 0.809V \quad (8)$$

$N = 39$, $R^2 = 0.778$, S.D. = 0.204, RMSE = 0.188, $F = 23.2$

Table 3
Values of log K_{brain} for air to human brain and air to rat brain partition

Compound	Brain (human)		Brain (rat)		Average
	log *K*	Reference	log *K*	Reference	log *K*
1,1,1-Trichloroethane	0.92	[3,9,6]			0.92
1,2,4-Trimethylbenzene			1.63	[15,16]	1.63
1,2,4-Trimethylcyclohexane			1.89	[15,16]	1.89
1,2-Dimethylcyclohexane			1.98	[15]	1.98
1,3-Butadiene	–0.08	[17]			–0.08
1-Butanol			3.06	[3]	3.06
1-Pentanol			3.03	[3]	3.03
1-Propanol	2.87	[3,9,6]	3.09	[3]	2.98
1-Octene			1.81	[18]	1.81
1-Nonene			2.04	[18]	2.04
1-Decene			2.17	[18]	2.17
2,2-Dimethylbutane	0.45	[3,9,6]			0.45
2-Methyl-1-propanol	2.61	[3,9,6]	2.94	[3]	2.78
2-Methylpentane	0.58	[3,9,6]			0.58
2-Methylheptane			1.35	[18]	1.35
2-Methyloctane			1.50	[18]	1.50
2-Methylnonane			1.81	[18]	1.81
2-Propanol	2.76	[3,9,6]	3.05	[3]	2.91
3-Methyl-1-butanol			2.79	[3]	2.79
3-Methylhexane	1.01	[3,9,6]			1.01
3-Methylpentane	0.64	[3,9,6]			0.64
4-Chlorobenzotrifluoride			1.60	[19]	1.60
Acetone	2.19	[3,9,6]			2.19
Argon	–1.49	[6]			–1.49
Benzene	1.26	[3,9,6]	1.24	[15]	1.25
Butan-2-one	2.07	[3,9,6]			2.07
Butyl acetate			2.22	[3]	2.22
Carbon disulfide	0.90	[6]			0.90
1,1-Difluoro-2-chloroethene	0.04	[9,6]			0.04
Halothane	0.77	[3,9,6]	0.65	[3]	0.71
Teflurane	0.05	[3,6]			0.05
2-Chloro-1,1,1-trifluoroethane	0.26	[3,9,6]			0.26
Fluroxene	0.29	[3,9,6]			0.29
Enflurane	0.49	[3,9,6]			0.49
Isoflurane	0.46	[3,9,6]	0.31	[15]	0.39
Sevoflurane	0.10	[3,9,6]			0.10
Trichloromethane	1.30	[3,9,6]			1.30
Cyclohexane	1.04	[3,9,6]	1.52	[15]	1.28
Cyclopropane	–0.10	[3,9]			–0.10
Decane			1.84	[15]	1.84
Dichloromethane	0.78	[3,9,6]			0.78
Diethyl ether	1.10	[3,9,6]			1.10
Divinyl ether	0.54	[3,9,6]			0.54
Ethanol	3.02	[3,9,6]	3.27	[3]	3.15
Ethyl acetate			1.90	[3]	1.90
Ethyl t-butyl ether			1.29	[20]	1.29
2-Methyl-2-propanol			2.79	[20]	2.79
Methyl t-butyl ether			1.54	[20]	1.54
Methyl t-pentyl ether			1.39	[20]	1.39
2-Methyl-2-butanol			2.66	[20]	2.66
Ethylene oxide	1.84	[21]	1.77	[22]	1.81
Ethene	–0.26	[21]	–0.19	[21]	–0.23

(continued)

Table 3 *(continued)*

Compound	Brain (human)		Brain (rat)		Average
	log *K*	Reference	log *K*	Reference	log *K*
Heptane	1.09	[3,9,6]	0.79	[15]	0.94
Hexane	0.70	[3,9,6]	1.07	[15]	0.89
Isobutyl acetate			2.14	[3]	2.14
Isopentyl acetate			2.34	[3]	2.34
Isopropyl acetate			1.95	[3]	1.95
Krypton	–1.38	[6]			–1.38
Methoxyflurane	1.41	[3,9,6]	1.39	[3]	1.40
Methane	–1.39	[6]			–1.39
Methyl acetate			1.85	[16]	1.85
Methylcyclopentane	0.86	[3,9,6]			0.86
Methylcyclohexane			1.66	[15]	1.66
Neon	–1.81	[6]			–1.81
Nitrogen	–1.80	[6]			–1.80
Nitrous oxide	–0.31	[9,6]			–0.31
Nonane			1.69	[15,16]	1.69
Octane	1.22	[3,6]	1.52	[15]	1.37
1,2-Dimethylbenzene			1.39	[15]	1.39
Pentane	0.34	[3,9,6]			0.34
Pentyl acetate			2.38	[3]	2.38
Propyl acetate			2.00	[3]	2.00
Propene	–0.22	[23]	–0.32	[23]	–0.27
Radon			–0.51	[24]	–0.51
Sulfur hexafluoride	–1.78	[6]			–1.78
t-Butylcyclohexane			1.77	[15]	1.77
t-Butylbenzene			1.67	[15]	1.67
Toluene	1.56	[3,9,6]	1.26	[15]	1.41
Trichloroethene	1.33	[3,9,6]	1.16	[25]	1.25
Xenon	–0.70	[9]			–0.70
Carbon dioxide	–0.25	[6]			–0.25

Table 4
Comparison of values of log K_{brain} for partition into human and rat brain

Statistic [a]	Value
N	17
AE	0.062
AAE	0.209
RMSE	0.245
S.D.	0.253

[a] *N* is the number of data points (compounds), AE is the average error, AAE is the average absolute error, RMSE is the root mean square error, and S.D. is the standard deviation.

Then from Eq. (8) we can predict values for the test set (A), to yield AE = 0.018, AAE = 0.159, S.D. = 0.210 and RMSE = 0.207 very similar to the predictions of test set (B).

We can combine the two sets and for the total set of 78 compounds obtain Eq. (9),

$$\mathrm{Log}P_{b-brain} = -0.057 + 0.017E - 0.536S - 0.323A - 0.335B + 0.731V \quad (9)$$

$N = 78$, $R^2 = 0.725$, S.D. = 0.203, RMSE = 0.196, $F = 37.9$

We have left out values for decane and cyclohexane, for which experimental and predicted values differed by –0.64 and 0.58 log units, respectively.

Our equations are capable of predicting further values of log $P_{b\text{-}brain}$ to around 0.20 log units, which must be close to the experimental error. Comparisons with previous work are in Table 2. The results in Table 2 illustrate how important it is to demonstrate the predictive capability of an equation through the stratagem of setting up a training set and an independent test set. Although equations have been reported with very small S.D. values, for example as low as 0.08 log units [10], these are only fitting equations and yield no information at all as to the predictive capability. Indeed, when the experimental error is likely to be about 0.2–0.3 log units, a fit of 0.08 log units suggests that there will be a considerable difference between the error in fits and the error in predictions.

Equations are thus available for the prediction of air to blood, air to brain and blood to brain partition coefficients. However, in order to implement these equations for actual predictions for other VOCs, the descriptors in Eqs. (2) and (3) are required. We have not listed the descriptors that we have used, because nearly all of them have been published previously [1].

Table 5
Values of air to brain, air to blood, and blood to brain partition coefficients for VOCs, as log K_{brain}, log K_{blood}, and log $P_{b\text{-}brain}$. Data are for log K_{blood} (human) and log K_{blood} (rat) averaged

Solute	log K_{brain} [a]	log K_{blood} [1]	log $P_{b\text{-}brain}$ [c]
1,1,1-Trichloroethane	0.92	0.63	0.29
1,2,4-Trimethylbenzene	1.63	1.47	0.16
1,2,4-Trimethylcyclohexane	1.89	0.87	1.02
1,2-Dimethylcyclohexane	1.98	0.91	1.07
1,3-Butadiene	–0.08	0.09	–0.17
1-Butanol	3.06	3.08	–0.02
1-Pentanol	3.03	2.83	0.20
1-Propanol	2.98	3.06	–0.08
1-Octene	1.81	1.07	0.74
1-Nonene	2.04	1.18	0.86
1-Decene	2.17	1.21	0.96
2,2-Dimethylbutane	0.45	–0.59	1.04
2-Methyl-1-propanol	2.78	2.92	–0.14
2-Methylpentane	0.58	–0.39	0.97
2-Methylheptane	1.35	0.49	0.86
2-Methyloctane	1.50	0.52	0.98
2-Methylnonane	1.81	0.76	1.05
2-Propanol	2.91	3.02	–0.11
3-Methyl-1-butanol	2.79	2.75	0.04
3-Methylhexane	1.01	0.11	0.90
3-Methylpentane	0.64	–0.37	1.01
4-Chlorobenzotrifluoride	1.60	1.43	0.17
Acetone	2.19	2.36	–0.17
Argon	–1.49	–1.52	0.03
Benzene	1.25	1.05	0.20
Butan-2-one	2.07	2.24	–0.17
Butyl acetate	2.22	1.94	0.28
Carbon disulfide	0.90	0.30	0.60
1,1-Difluoro-2-chloroethene	0.04	0.06	–0.02
Halothane	0.71	0.57	0.14
Teflurane	0.05	–0.22	0.27
1-Chloro-2,2,2-trifluoroethane	0.26	0.14	0.12
Fluroxene	0.29	0.15	0.14
Enflurane	0.49	0.35	0.14
Isoflurane	0.39	0.20	0.19
Sevoflurane	0.10	–0.20	0.30
Trichloromethane	1.30	1.15	0.15
Cyclopropane	–0.10	–0.21	0.11
Dichloromethane	0.78	1.12	–0.34
Diethyl ether	1.10	1.11	–0.01
Divinyl ether	0.54	0.41	0.13
Ethanol	3.15	3.27	–0.12
Ethyl acetate	1.90	1.90	0.00
Ethyl t-butyl ether	1.29	1.07	0.22
2-Methyl-2-propanol	2.79	2.68	0.11
Methyl t-butyl ether	1.54	1.18	0.36
Methyl t-pentyl ether	1.39	1.22	0.17
2-Methyl-2-butanol	2.66	2.59	0.07
Ethylene oxide	1.81	1.80	0.01
Ethene	–0.23	–0.53	0.31
Heptane	0.94	0.50	0.44
Hexane	0.89	0.21	0.68
Isobutyl acetate	2.14	1.69	0.45
Isopentyl acetate	2.34	1.79	0.55
Isopropyl acetate	1.95	1.55	0.40
Krypton	–1.38	–1.22	–0.16
Methoxyflurane	1.40	1.28	0.12
Methane	–1.39	–1.42	0.03
Methyl acetate	1.85	1.98	–0.13
Methylcyclopentane	0.86	–0.07	0.93
Methylcyclohexane	1.66	0.70	0.96
Neon	–1.81	–2.01	0.20
Nitrogen	–1.80	–1.83	0.03
Nitrous oxide	–0.31	–0.34	0.03
Nonane	1.69	1.17	0.52
Octane	1.37	0.68	0.69
1,2-Dimethylbenzene	1.39	1.42	–0.03
Pentane	0.34	–0.29	0.63
Pentyl acetate	2.38	1.98	0.40
Propyl acetate	2.00	1.88	0.12
Propene	–0.27	–0.21	–0.06
Radon	–0.51	–0.39	–0.12
Sulfur hexafluoride	–1.78	–2.17	0.39
t-Butylcyclohexane	1.77	1.16	0.61
t-Butylbenzene	1.67	1.24	0.43
Toluene	1.41	1.14	0.27
Trichloroethene	1.25	1.14	0.11
Xenon	–0.70	–0.85	0.15

[a] From Table 3.
[c] From the previous two columns.

As regards prediction of further values of log K_{brain} and log $P_{b\text{-}brain}$ the necessary descriptors are available for over 3000 compounds and can be calculated just from structure [14]. Hence the various partition coefficients can now easily be predicted.

We have chosen to average the human and rat data and then to analyze the averaged data for log K_{brain} and log $P_{b\text{-}brain}$. However, it would be possible to combine the data differently in order to obtain log $P_{b\text{-}brain}$ for rat and human separately. We have been careful to reference the rat and human data so that any analysis of log $P_{b\text{-}brain}$ (rat) and log $P_{b\text{-}brain}$ (human) can be carried out separately, if required.

3.3. Discussion on coefficients in the LFERs

The coefficients in the LFERs, Eqs. (2) and (3), are not just fitting coefficients, but contain information of the chemical properties of the phases involved. Eq (2) is the simpler to discuss, because the coefficients refer to the difference between properties of the gas phase and the condensed phase, whereas the coefficients in Eq. (3) refer to the difference in properties of two condensed phases. We therefore concentrate on the equations derived from Eq. (2). Values of the coefficients for a number of air to phase processes are collected in Table 6. For air to blood, the s-, a-, b- and l-coefficients are all positive, as

they should be. Any interaction between VOCs and the condensed phase must aid the gaseous solubility and so make a positive contribution to log K_{brain} and log K_{blood}. The numerical values of the coefficients indicate specific chemical properties of the phases that lead to interactions with the VOCs. In particular, both blood and brain must be highly dipolar (s-coefficient very positive), strong hydrogen bond bases (a-coefficient very positive), and strong hydrogen bond acids (b-coefficient very positive). These coefficients are not as large as those for water, but are still substantial by comparison to those for organic solvents, see Table 6. On the other hand, the l-coefficients for blood and brain are considerably less than those for organic solvents, and indicate that blood, especially, has hydrophilic/hydrophobic properties much nearer to water than those for organic solvents. Table 6 contains coefficients for a number of phases that might be considered as 'model' phases for blood and brain, such as octan-1-ol and olive oil. Neither of these is very close to blood or brain, and olive oil, indeed, is very far away in chemical terms.

On comparing coefficients for air to phase processes, those we have obtained in equations for air to blood and air to brain seem chemically reasonable. They indicate that the equations we have suggested for correlation and prediction, on the lines of Eq. (2) are not just fitting equations, but encode chemical information about blood and brain phases.

3.4. Air to plasma and plasma to brain partition coefficients

There are available data on air to plasma partition coefficients, K_{plasma}, for 36 VOCs [6,27] as shown in Table 7. These are just enough data to construct a training set, but not enough for both a training and a test set. The resulting equation for the 36 VOCs is

$$\mathrm{Log}K_{plasma} = -1.435 + 0.543E + 1.677S + 3.518A + 3.982B + 0.192L \quad (10)$$

$N = 36$, $R^2 = 0.979$, S.D. = 0.249, RMSE = 0.227, $F = 285.4$

This equation is somewhat different from the equation for air to blood distribution that we have previously constructed [1]:

$$\log K_{blood}(\text{human or rat}) = -1.069 + 0.456E + 1.083S + 3.738A + 2.580B + 0.376L \quad (11)$$

Table 6
Coefficients in the LFER, Eq. (3), for air to various phases at 25 °C, and for air to blood and air to brain at 37 °C

Solvent	c	e	s	a	b	l
Water	–1.271	0.822	2.743	3.904	4.814	–0.213
Blood (human and rat)	–1.069	0.456	1.083	3.738	2.580	0.376
Brain (human and rat)	–0.987	0.263	0.411	3.358	2.025	0.591
Octan-1-ol (wet)	–0.198	0.002	0.709	3.519	1.429	0.858
Octan-1-ol	–0.120	–0.203	0.560	2.560	0.702	0.939
N-Methylformamide	–0.599	–0.259	2.003	4.559	0.430	0.706
Olive oil	–0.230	0.009	0.795	1.353	0.000	0.888
Plant cuticle	–0.617	0.082	1.282	3.120	0.820	0.860

Table 7
Air to plasma distribution for VOCs, [a,b] as log K_{plasma}

Solute	log K_{plasma}
Helium	–2.07
Argon	–1.58
Krypton	–1.29
Xenon	–1.04
Hydrogen	–1.76
Oxygen	–1.61
Nitrogen	–1.87
Nitrous oxide	–0.34
Methane	–1.59
Ethane [a,b]	–1.39
Cyclopropane[a,b]	–0.63
Acetylene	–0.11
Fluoroethane	0.07
Fluoromethane	0.01
1-Fluoropropane	–0.01
2-Fluoropropane	0.00
Iodoethane	0.69
Fluorotrichloromethane	–0.12
Difluorodichloromethane	–1.07
Halothane	0.40
1,2-Dichlorotetrafluoroethane	–0.66
Dimethyl ether	1.12
Diethyl ether [a,b]	1.12
Methoxyflurane	1.00
Isoflurane	0.20
Fluroxene	0.05
Enflurane [b]	0.00
Acetone [a,b]	2.37
Butanone	2.12
Methanol	3.27
Ethanol	3.16
1-Propanol	2.99
2-Propanol	2.91
2-Methyl-1-propanol	2.77
Sulfur hexafluoride[a,b]	–2.35
Carbon disulfide	–0.10

[a] All log K (human) values from Abraham and Weathersby [6] unless noted otherwise.
[b] log K (rat) values from Guitart [27].

$N = 196$, $R^2 = 0.938$, S.D. = 0.324, RMSE = 0.319, $F = 572.8$

The reason might be because of a fundamental difference between blood and plasma, or it could arise because of a restricted and possibly unrepresentative data set for log K_{plasma}. In order to resolve this, we have compared experimental data for air to blood and air to plasma for 35 common compounds. Details of the comparisons are in Table 8. The best indication of agreement, or disagreement, is the average error, AE, which is only 0.116 log unit, and which suggests that any difference between air to blood and air to plasma partition coefficients for this set of compounds is rather small. Combination of air to blood and air to plasma partition data is equivalent to assuming that the blood to plasma concentration ratio equals unity, which is an approx-

imation often made in pharmacokinetic modeling. Published studies [28–34] have shown that for many drug molecules the measured blood to plasma concentration ratios typically fall in the 0.65–1.50 range. On a logarithmic sale, this corresponds to a difference of less than 0.2 log units. The above observations suggest that air to blood and air to blood plasma data can be combined. The equation for the combined sets is

$$\log K_{\text{blood or plasma}}(\text{human or rat}) = -1.154 + 0.446E + 1.130S + 3.844A + 2.673B + 0.386L \quad (12)$$

$N = 232$, $R^2 = 0.943$, S.D. = 0.332, RMSE = 0.328, $F = 741.6$

From the data on air to plasma, Table 6, and on air to brain, Table 4, we can deduce values for partition between plasma and brain for 21 VOCs. There are 19 common compounds with data on partition between blood and brain, and statistics on this 19 compound data set are in Table 8. The definitions of AE, AAE, RMSE and S.D. are as given before, in connection with Table 4, and the interpretation is similar. The value of AE indicates the systematic difference between partition between plasma and brain and blood and brain, and is only 0.120 log unit. On the other hand, the random error in the two sets of measurements, given by RMSE and S.D. is much larger, at 0.164 or 0.168 log units. The statistics are almost the same as for comparison between the log K values, and suggest that the systematic difference of 0.116 log unit between log K_{blood} and log K_{plasma} is carried forward into the log $P_{\text{b-brain}}$ and log $P_{\text{p-brain}}$ values. This difference is rather less than the experimental error in log $P_{\text{b-brain}}$, which must be around 0.17 log unit as shown by the RMSE and S.D. values in Table 8, so that it is probably permissible to combine the data sets to yield 99 values of the partition coefficient for blood or plasma to brain, log $P_{\text{bp-brain}}$. As usual, we divide these into a training set, of 50 data points, and a test set of 49 data points. The training set yields the equation

$$\log P_{\text{bp-brain}}(\text{human or rat}) = 0.023 + 0.074E - 0.655S - 0.177A - 0.283B + 0.652V \quad (13)$$

$N = 50$, $R^2 = 0.700$, S.D. = 0.206, RMSE = 0.193, $F = 20.5$

Eq. (13) can then be used to predict values for the 49 data point test set, giving AE = 0.003, AAE = 0.151, S.D. = 0.197 and RMSE = 0.195 log units. Finally, the total data set yields Eq. (14),

$$\log P_{\text{bp-brain}}(\text{human or rat}) = -0.028 + 0.003E - 0.485S - 0.117A - 0.408B + 0.703V \quad (14)$$

$N = 99$ (80 compounds), $R^2 = 0.703$, S.D. = 0.197, RMSE = 0.191, $F = 44.1$

The full equations, Eqs. (9) and (14), are not substantially different, and the statistics are almost the same. It is a moot point as to whether further values of blood to brain partition coefficients should best be predicted through Eq. (9) or (14). We slightly prefer Eq. (9) because it refers specifically to blood rather than to blood or plasma.

Table 8
Comparison of air to blood and air to plasma partitions as log K, and blood to brain and plasma to brain partitions, as log P

Statistic[a]	log K	log P
N	35	19
AE	0.116	0.120
AAE	0.127	0.122
RMSE	0.172	0.164
S.D.	0.174	0.168

[a] N is the number of data points (compounds), AE is the average error, AAE is the average absolute error, RMSE is the root mean square error, and S.D. is the standard deviation.

4. Conclusions

We have collected enough data from the literature to be able to show that partitions from the gas phase to human brain and to rat brain for VOCs may be combined. These partitions can then be averaged and yield values of log K_{brain} for 81 VOCs. A multiple linear regression equation for the 81 VOCs can predict further values of log K_{brain} to about 0.4 log unit, as shown in Table 1. This is the first time that any assessment of the predictive capability of an equation for log K_{brain} has been reported.

The log K_{brain} values can be combined with values of log K_{blood} that refer to partition from the gas phase to human blood and rat blood, to yield log P_{blood} values for the partition of VOCs from human and rat blood to human and rat brain for 78 VOCs. Multiple linear regression equations show that further values can be predicted to 0.20 log units, again the first time that any assessment of predictive capability has been made.

It is further shown that data on partition from the gas phase to blood and from the gas phase to plasma may be combined, and these data yield additional values for an equation for partition from human plasma and blood, and rat plasma and blood, to human and rat brain for 80 VOCs (99 data points). This is an alternative equation to the one that refers specifically to partition from human and rat blood to human and rat brain, although the difference is minimal.

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