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Original article

Air to liver partition coefficients for volatile organic compounds and blood to liver partition coefficients for volatile organic compounds and drugs

Michael H. Abraham [a,*], Adam Ibrahim [a], William E. Acree Jr. [b]

[a] *Department of Chemistry, University College London, 20 Gordon Street, London, Middlesex WC1H OAJ, UK*
[b] *Department of Chemistry, P.O. Box 305070, University of North Texas, Denton, TX 76203-5070, USA*

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Abstract

Values of *in vitro* air to liver partition coefficients, K_{liver}, of VOCs have been collected from the literature. For 124 VOCs, application of the Abraham solvation equation to $\log K_{liver}$ yielded a correlation equation with $R^2 = 0.927$ and SD = 0.26 log units. Combination of the $\log K_{liver}$ values with $\log K_{blood}$ values leads to *in vitro* blood to liver partition coefficients, as $\log P_{liver}$ for VOCs; an Abraham solvation equation can correlate 125 such values with $R^2 = 0.583$ and SD = 0.23 log units. Values of *in vivo* $\log P_{liver}$ for 85 drugs were collected, and were correlated with $R^2 = 0.522$ and SD = 0.42 log units. When the $\log P_{liver}$ values for VOCs and drugs were combined, an Abraham solvation equation could correlate the 210 compounds with $R^2 = 0.544$ and SD = 0.32 log units. Division of the 210 compounds into a training set and a test set, each of 105 compounds, showed that the training equation could predict $\log P_{liver}$ values with an average error of 0.05 and a standard deviation of 0.34 log units.
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Keywords: Volatile organic compounds; Drugs; Liver; Blood-liver; Plasma-liver; Partition coefficients; Linear free energy relationship; Abraham equation

1. Introduction

Partition coefficients from air to tissue and from blood to tissue are of importance in environmental and toxicological modelling, and in pharmacokinetics modelling. Not surprisingly, there are a very large number of studies in which these partition coefficients have been measured. In the particular case of partition coefficients from air to liver, K_{liver}, there are numerous citations for volatile organic compounds, VOCs [1–24]. One purpose of this work is to collect a comprehensive set of values of K_{liver} in order to construct an equation for the prediction of further values. The complete list of log K_{liver} values for VOCs is in Table 1; note that Zahlsen et al. [5,6,18] gave quantities in blood and in liver, which lead to blood to liver partition coefficients rather than air to liver. We have included a few volatile inorganic compounds in the list, but we shall refer collectively to the list as 'VOCs'. In Table 1 we enter data for partition into rat liver and human liver separately. All of this data have been obtained by measurements using liver *in vitro*.

Although there have been a very large number of reports on air to liver partitioning, only few attempts to correlate and predict $\log K_{liver}$ values. Meulenberg and Vijverberg [1] found that partition coefficients of VOCs in human (or rat) liver are well described by a linear combination of air to oil and air to saline partition coefficients, K_{oil} and K_{saline} as Eqs. (1) and (2).

$$K_{liver}(\text{human}) = 0.028K_{oil} + 0.79$$

$$N = 28,\ R^2 = 0.88,\ \text{SD} = n/a,\ F = n/a \quad (1)$$

* Corresponding author. Tel.: +44 020 7679 4639; fax: +44 020 7679 7463.
E-mail address: m.h.abraham@ucl.ac.uk (M.H. Abraham).

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Table 1
Air to liver partition, as log K_{liver}, and blood to liver distribution, as log P_{liver}, of VOCs

Solute	Log K_{liver}					Log P_{liver}
	Human	Reference	Rat	Reference	Average	
Krypton	−1.14	[4]			−1.14	0.08
Xenon	−1.00	[2]			−1.00	−0.15
Radon			−0.51	[12]	−0.51	−0.12
Nitrous oxide	−0.38	[2,4]			−0.38	−0.04
Pentane	0.32	[1,2,4]			0.32	0.61
Hexane	0.72	[1,2,4]	0.65	[1,3]	0.69	0.48
Heptane	1.04	[1,2,4]	0.87	[1,3]	0.96	0.46
Octane	1.41	[1,4]			1.41	0.73
Nonane						0.50[a]
Decane					2.09[b]	0.85[a]
2-Methylpentane	0.65	[1,2,4]			0.65	1.04
3-Methylpentane	0.69	[1,2,4]			0.69	1.06
3-Methylhexane	1.04	[1,2,4]			1.04	0.93
2-Methylheptane					0.75[c]	0.52[c]
2-Methyloctane					1.17[c]	0.74[c]
2-Methylnonane					1.45[c]	0.76[c]
2,2-Dimethylbutane	0.54	[1,2,4]			0.54	1.13
2,2,4-Trimethylpentane			1.03	[1,3]	1.03	0.80
2,3,4-Trimethylpentane			1.27	[1,3]	1.27	0.70
Cyclopropane					−0.19	0.02
Methylcyclopentane	0.89	[1,2,4]			0.89	0.96
Cyclohexane	1.03	[1,2,4]	1.06	[1,3]	1.05	0.88
Methylcyclohexane					1.09[a,d]	0.71[a]
1,2-Dimethylcyclohexane					1.74[a]	1.17[a]
1,2,4-Trimethylcyclohexane					1.54[a]	0.86[a]
tert-Butylcyclohexane					1.68[a]	0.30[a]
JP-10			2.74	[3]	2.74	0.98
Ethene	−0.35	[20]	−0.24	[20]	−0.30	0.24
Propene	−0.27	[10]	−0.29	[10]	−0.28	−0.07
1-Octene					1.35[c]	0.80[c]
1-Nonene					1.71[c]	0.93[c]
1-Decene					1.98[c]	1.06[c]
1,3-Butadiene	−0.17	[8]			−0.17	−0.26
2-Methyl-1,3-butadiene			0.42	[1,3,17]	0.42	0.32
Difluoromethane			0.44	[1,3]	0.44	0.24
Chloromethane			0.54	[1,3]	0.54	0.23
Dichloromethane	0.86	[1,2,4]	1.15	[1,3]	1.01	−0.11
Chloroform	1.23	[1,2,4]	1.32	[1,3]	1.28	0.13
Carbon tetrachloride			1.15	[1,3]	1.15	0.53
Chloroethane			0.56	[1,3]	0.56	0.07
1,1-Dichloroethane			1.03	[1,3]	1.03	0.15
1,2-Dichloroethane			1.55	[1,3]	1.55	0.16
1,1,1-Trichloroethane	1.21	[1,2,4]	0.93	[1,3]	1.07	0.44
1,1,2-Trichloroethane			1.86	[1,3]	1.86	0.19
1,1,1,2-Tetrachloroethane			1.95	[1,3]	1.95	0.40
1,1,2,2-Tetrachloroethane			2.29	[1,3]	2.29	0.16
Pentachloroethane			2.41	[1,3]	2.41	0.39
Hexachloroethane			2.57	[1,3]	2.57	0.81
1-Chloropropane			0.71	[1,3]	0.71	0.12
2-Chloropropane			0.50	[1,3]	0.50	0.18
1,2-Dichloropropane			1.39	[1,3]	1.39	0.25
Dibromomethane			1.83	[1,3]	1.83	−0.04
1,2-Dibromoethane			2.08	[1,3]	2.08	0.00
1-Bromopropane			0.91	[1,3]	0.91	−0.06
2-Bromopropane			0.64	[1,3]	0.64	0.00
Fluorochloromethane			0.54	[1,3]	0.54	−0.17
Bromochloromethane			1.47	[1,3]	1.47	0.26
Bromodichloromethane			1.49	[22]	1.49	0.00
Chlorodibromomethane			2.10	[1,3]	2.10	0.22
1,1-Dichloro-1-fluoroethane			0.52	[15]	0.52	0.20
1-Bromo-2-chloroethane			1.63	[1,3]	1.63	0.03

Table 1 (*continued*)

Solute	Log K_{liver}					Log P_{liver}
	Human	Reference	Rat	Reference	Average	
2-Chloro-1,1,1-trifluoroethane	0.36	[1,2,4]	0.26	[1,3]	0.31	0.17
2,2-Dichloro-1,1,1-trifluoroethane			0.67	[16]	0.67	0.06
1,1-Difluoroethene			−0.10	[14]	−0.10	0.64
Chloroethene	0.20	[21]	0.20	[1,3,21]	0.20	0.03
1,1-Dichloroethene			0.65	[1,3]	0.65	−0.05
cis-1,2-Dichloroethene			1.18	[1,3]	1.18	0.02
trans-1,2-Dichloroethene			0.95	[1,3]	0.95	0.07
Trichloroethene	1.41	[1,2,4]	1.40	[1,3,19]	1.41	0.27
Tetrachloroethene			1.85	[1,3]	1.85	0.66
Bromoethene			0.52	[1,3]	0.52	0.03
1-Chloro-2,2-difluoroethene	0.04	[2,4]			0.04	−0.02
1,2-Epoxy-3-butene			1.74	[23]	1.74	−0.23
1-Propanol			3.11	[1]	3.11	0.05
2-Propanol			2.99	[1]	2.99	−0.03
1-Butanol			3.10	[1]	3.10	0.02
2-Methyl-1-propanol			2.94	[1]	2.94	0.02
tert-Butanol			2.69	[9,24]	2.69	0.01
1-Pentanol			3.24	[1]	3.24	0.41
3-Methyl-1-butanol			2.97	[1]	2.97	0.22
tert-Amyl alcohol			2.68	[9]	2.68	0.09
Acetone			2.38	[1]	2.38	0.02
Butanone			2.36	[1]	2.36	0.12
2-Pentanone			2.27	[1]	2.27	0.13
4-Methyl-2-pentanone			2.19	[1]	2.19	0.23
2-Heptanone			2.63	[1]	2.63	0.30
Methyl acetate			1.95	[1]	1.95	−0.03
Ethyl acetate			2.03	[1]	2.03	0.13
Propyl acetate			2.36	[1]	2.36	0.48
Isopropyl acetate			2.17	[1]	2.17	0.62
Butyl acetate			2.45	[1]	2.45	0.51
Isobutyl acetate			2.42	[1]	2.42	0.73
Pentyl acetate			2.64	[1]	2.64	0.66
Isopentyl acetate			2.55	[1]	2.55	0.76
Diethyl ether	1.05	[1,2,4]	0.83	[1,3]	0.94	−0.17
tert-Butyl methyl ether			1.35	[9,24]	1.35	0.17
tert-Butyl ethyl ether			1.52	[9]	1.52	0.45
tert-Amyl methyl ether			1.50	[9]	1.50	0.28
Divinyl ether	0.48	[1,2,4]			0.48	0.07
Ethylene oxide	1.73	[20]			1.73	−0.07
Cyanoethylene oxide			2.66	[7]	2.66	−0.56
Halothane	0.86	[1,2,4]	0.86	[1,3,16]	0.86	0.29
Teflurane	0.01	[1,4]			0.01	0.23
Fluomar/fluroxene	0.33	[1,2,4]			0.33	0.18
Enflurane	0.62	[1,2,4]			0.62	0.27
Isoflurane	0.55	[1,2,4]	0.57	[1,3]	0.56	0.36
Sevoflurane	0.43	[1,2,4]			0.43	0.63
Methoxyflurane	1.46	[1,2,4]	1.47	[1]	1.47	0.19
1-Nitropropane			2.18	[1,3]	2.18	−0.13
2-Nitropropane			1.80	[1,3]	1.80	−0.43
Carbon disulfide	0.78	[4]			0.78	0.48
Benzene	1.36	[1,2,4]	1.15	[1,3]	1.26	0.21
Toluene	1.68	[1,2,4]	1.60	[1,3]	1.64	0.50
Ethylbenzene			1.78	[1]	1.78	0.31
o-Xylene			1.76	[1,3]	1.76	0.34
m-Xylene			1.96	[1,3]	1.96	0.37
p-Xylene			1.95	[1,3]	1.95	0.34
1,2,4-Trimethylbenzene					2.20[a,c]	0.43[a]
tert-Butylbenzene					2.32[a]	0.49[a]
Styrene			2.14	[1,3]	2.14	0.47
m-Methylstyrene			2.51	[1,3]	2.51	0.23
p-Methylstyrene			2.51	[1,3]	2.51	0.14

(*continued on next page*)

Table 1 (*continued*)

Solute	Log K_{liver}					Log P_{liver}
	Human	Reference	Rat	Reference	Average	
Chlorobenzene			1.94	[1,3]	1.94	0.31
4-Chlorobenzotrifluoride			1.71	[13]	1.71	0.28
Furan			0.77	[11]	0.77	−0.05

[a] Refs. [6,18].
[b] From air to blood partition coefficient of 17.3, Ref. [1].
[c] Ref. [5].
[d] From air to blood partition coefficient of 5.0, Ref. [1].
[e] From air to blood partition coefficient of 59.1, Ref. [1].

$$K_{liver}(\text{rat}) = 0.026K_{oil} + 0.878K_{saline} + 2.36$$

$$N = 77,\ R^2 = 0.92,\ \text{SD} = n/a,\ F = n/a \quad (2)$$

N is the number of data points, usually the number of compounds, R is the correlation coefficient, SD is the standard deviation, RMSE is the root mean square deviation, and F is the F-statistic. Unfortunately, no predictive assessment of the equations was made.

Gargas et al. [3] also modelled VOC air to rat liver distribution in terms of contributions from air to oil and air to saline. Reasonable fits were obtained, Eq. (3) but again no predictive assessment was made.

$$\text{Log}\, K_{liver}(\text{rat}) = 0.730 \log K_{oil} + 0.128K_{saline} - 0.550$$

$$N = 55,\ R^2 = 0.903,\ \text{SD} = n/a,\ \text{RMSE} = 0.217,\ F = n/a \quad (3)$$

Poulin and Krishnan [25] set out a system for the prediction of air to tissue partition coefficients, including rat liver. They first use a standard equation, $K_{liver} = C_{tissue}/C_{gas}$, where C_{gas} is the saturated vapour concentration, obtained from the saturated vapour pressure of the VOC at 310 K, and C_{tissue} is the solubility of the VOC in the tissue. The saturated vapour concentration has to be available, and the solubility is calculated from the known solubility in water (or saline) and in vegetable oil. There are only two adjustable constants that are the same for all tissues, the difference between tissues being a function of the amount of water, neutral lipid and phospholipids in the tissue. Thus the calculation of values of K_{liver} by this method is almost a prediction. For 45 VOCs, Poulin and Krishnan showed that the ratio K_{liver} (predicted)/K_{liver} (experimental) was 0.94 for air to rat liver partition. This is not a very informative statistic and so we have used the data of Poulin and Krishnan [25] to calculate that for the 45 VOCs, when the predicted and experimental values are transformed into logarithms, the average error in $\log K_{liver}$(AE) = −0.07, the average absolute error (AAE) = 0.167, the RMSE = 0.224 and the SD = 0.266 log units. In a further development, Krishnan et al. [26] calculated $\log K_{liver}$(rat) for 46 very simple VOCs by using a fragment based scheme, and obtained $R^2 = 0.973$; however, 11 descriptors (fragments) were needed for the 46 VOCs. In a combination of the two methods, Krishnan et al. [27] used the same fragment method to calculate air to water, air to oil and air to protein partition coefficients, and then combinations of these calculated coefficients to obtain various air to tissue partition coefficients, including K_{liver}. For 46 VOCs a plot of calculated vs observed $\log K_{liver}$ values had $R^2 = 0.8689$.

The only methods used to calculate $\log K_{liver}$ that gave an assessment of predictive capability are those of Katritzky et al. [28]. In the first method, 780 molecular descriptors were calculated, and four of them were used to correlate $\log K_{liver}$(human). The equation had $N = 34$, $R^2 = 0.881$, SD = 0.207 log units and $F = 46.4$; a very small test set of 10 compounds had SD = 0.226 log units. Five molecular descriptors were used to correlate $\log K_{liver}$(rat), leading to an equation with $N = 100$, $R^2 = 0.906$, SD = 0.303 log units and $F = 180.9$; a test set of 33 compounds had SD = 0.307 log units. The second method was a fragmentation scheme. For $\log K_{liver}$(human), a scheme with nine fragments correlated 30 values with $R^2 = 0.915$, SD = 0.090 log units and $F = 28.3$; no test set was used. For the 100 values of $\log K_{liver}$(rat), 21 fragments were used, $R^2 = 0.939$, SD = 0.270 log units and $F = 60.4$; a test set of 32 compounds had SD = 0.360 log units.

For *in vitro* blood to liver partition, the number of correlative methods is even less. Abraham and Weathersby [4] correlated 28 values of $\log P_{liver}$(human) for VOCs with the Abraham descriptors (see below) and found $R^2 = 0.865$ and SD = 0.155 log units. More complicated expressions were used by Balaz and Luckacova [29] and by Zhang [30]. The former workers used the water to octanol partition coefficient, as $\log P_{oct}$, together with adjustable parameters A_0, A_1, A_2, A_b and β, and indicator variables I_1 for alcohols and I_2 for alkanes. A_0 was not significant, but six adjustable variables were used to correlate values for 28 simple compounds, so that it is not surprising that the statistics for the fitting equation were good, $R^2 = 0.931$, SD = 0.095 log units and $F = 108.3$; no assessment of predictive ability was made. Zhang [30] set out two initial equations to calculate $\log P_{lipid}$ and $\log P_{protein}$, using as descriptors, α the molecular polarizability, $\sum$Ca the sum of H-bond factor values for all hydrogen bond acceptor substructures in the molecule and $\sum Q^+$ the sum of all positive partial atomic charges for all atoms in the molecule. These were then combined non-linearly to calculate $\log P_{liver}$(human). For 29 simple VOCs, the fitting equation had $R^2 = 0.872$ and SD = 0.134 log

units; once again, no predictive assessment was made. Zhang and Zhang [31] examined *in vivo* data of drugs for partition between blood and several tissues, and obtained a general training equation that covered 248 data points over seven tissues. For blood to liver, however, there were only 24 drugs in the 248 data points, and only five drugs in an independent test set. For the given predicted and experimental values of $\log P_{liver}$ [31], we calculate that AE = 0.23, AAE = 0.48, RMSE = 0.50 and SD = 0.56 log units on one equation, and AE = 0.18, AAE = 0.46, RMSE = 0.49 and SD = 0.55 log units on a second equation. AE is the average error, a measure of any bias in predictions, and AAE is the absolute average error. Although these results are only for five drugs, the large value of the standard deviation error indicates the difficulty in predicting *in vivo* blood to liver distribution.

Poulin and Theil [32] have also set out a general equation for the prediction of *in vivo* plasma to tissue partition coefficients of drugs, but unfortunately not for plasma to liver, and have also predicted a few *in vivo* $\log P_{liver}$ values [33], but there are no experimental values to compare them.

Thus, the only assessments of predictive capability using independent test sets, of any equation for $\log K_{liver}$ or $\log P_{liver}$, are those of Katritzky et al. [28] for *in vitro* $\log K_{liver}$(human) for which $N = 10$ and SD = 0.226 log units, and for *in vitro* $\log K_{liver}$(rat) for which $N = 33$ and SD = 0.307 log units or $N = 32$ and SD = 0.360 log units, and those of Zhang and Zhang [31] for *in vivo* $\log P_{liver}$ for which $N = 5$ and SD = 0.55 log units. It is the aim of this work to set out a comprehensive list of $\log K_{liver}$ or $\log P_{liver}$ values, to obtain equations that correlate these values and to assess the predictive capability of the equations.

2. Methods

We use the same methods that we have previously employed [34–41] for partition from air to blood [34], air to brain [35], blood to brain [36], air and blood to muscle [37], and air and blood to fat [38]. In brief, the equations that we use are given as Eqs. (4) and (5),

$$SP = c + e{\cdot}E + s{\cdot}S + a{\cdot}A + b{\cdot}B + l{\cdot}L \quad (4)$$

$$SP = c + e{\cdot}E + s{\cdot}S + a{\cdot}A + b{\cdot}B + v{\cdot}V \quad (5)$$

In these equations [34–40] SP is the dependent variable. Eq. (4) is used to correlate air to tissue or air to solvent partitions, and in the present case SP is then $\log K_{liver}$. Eq. (5) is used to correlate partition from one condensed phase to another, and in the present case SP is then $\log P_{liver}$. The independent variables in Eqs. (4) and (5) are properties of VOCs and drugs, as we have discussed before [33–40]. 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 $(dm^3\ mol^{-1})/100$.

The experimental data on $\log K_{liver}$ values [1–24] that we use are summarized in Table 1 for 114 VOCs; values for *in vitro* partition into human liver and rat liver are given separately and the final column is the average of the human and rat values.

The *in vitro* air to liver $\log K_{liver}$(human/rat) values, Table 1, can be combined with *in vitro* air to blood partition coefficients, as $\log K_{blood}$(human/rat), that we have previously reported [34] to give *in vitro* blood to liver distributions for VOCs as $\log P_{liver}$(human/rat). Values of $\log P_{liver}$(human/rat) are given in Table 1 and are indirect *in vitro* values, except for the VOCs studied by Zahlsen et al. [5,6,18] that are *in vivo* values. However, we keep these in the same set as the other VOCs as well as the indirect *in vitro* $\log P_{liver}$ values for VOCs. There are a large number of direct *in vivo* values, nearly all for distribution from blood or plasma or serum to rat liver. These are listed in Table 2, together with *in vivo* values for distribution to human liver [42–71]. As before, for distribution to brain [35] and muscle [37], we take distribution from blood, plasma and serum together, although they are separately listed in Table 2. There are a few compounds in Table 1 and Table 2 that are difficult to identify, and their SMILES notation is given in Table 3.

3. Results and discussion

3.1. Air to liver distribution

Nearly all previous workers have correlated the *in vitro* $\log K_{liver}$(human) or $\log K_{liver}$(rat) values separately. However, we have shown previously that for air to brain [35] and air to muscle [37] partition coefficients, the data for human tissue and rat tissue were so close, that they could be combined. In Table 1, there are 18 compounds for which both $\log K_{liver}$(human) and $\log K_{liver}$(rat) values are available. For these 18 sets of values we find that AE = 0.057, AAE = 0.118, RMSE = 0.167 and SD = 0.172 log units. The AE shows how close the two sets are, and within any reasonable experimental error the two sets can be taken as the same, and the $\log K_{liver}$(human) and $\log K_{liver}$(rat) values averaged; this has been shown in Table 1. The AAE, the RMSE and the SD are all measures of random error, and suggest that the experimental error in $\log K_{liver}$ is around 0.17 log units.

We therefore average the human and rat $\log K_{liver}$ values, and correlate the averaged values against our descriptors as in Eq. (4) to yield Eq. (6); the term $e{\cdot}E$ was statistically not significant and has been removed.

$$\begin{aligned}\text{Log}\,K_{liver}(\text{human/rat, } \textit{in vitro}) &= -0.943(0.069) + 0.836(0.099)S + 2.836(0.258)A \\ &\quad +2.081(0.137)B + 0.564(0.021)L\end{aligned}$$

$$N = 124,\ R^2 = 0.927,\ R^2_{CV} = 0.924,\ SD = 0.256,\ F = 376.8 \quad (6)$$

In Eq. (6), R^2_{CV} (sometimes denoted as Q^2) is the square of the leave-one-out cross validated correlation coefficient. There is

Table 2
Blood, plasma or serum to liver distribution, as log P_{liver}, of drugs[a]

Solute	Log P_{liver}	System	Reference
1-(3-Fluoropropyl)-2-nitroimidazole	0.92	Blood	[42]
1-(8-fluorooctyl)-2-nitroimidazole	0.47	Blood	[42]
4-Chlorobiphenyl	0.00	Blood	[43]
4,4′-Dichlorobiphenyl	0.48	Blood	[43]
3,3′,5,5′-Tetrachlorobiphenyl	0.78	Blood	[44]
2,2′,4,5,5′-Pentachlorobiphenyl	0.78	Blood	[43]
2,2′,4,4′,5,5′-Hexachlorobiphenyl	1.08	Blood	[43]
5-Methyl-5-ethyl barbituric acid	0.44	Plasma	[45]
5-Ethyl-5-ethyl barbituric acid	0.57	Plasma	[45]
5-Propyl-5-ethyl barbituric acid	0.47	Plasma	[45]
5-Butyl-5-ethyl barbituric acid	0.47	Plasma	[45]
5-Pentyl-5-ethyl barbituric acid	0.51	Plasma	[45]
5-Hexyl-5-ethyl barbituric acid	0.44	Plasma	[45]
5-Heptyl-5-ethyl barbituric acid	0.15	Plasma	[45]
5-Octyl-5-ethyl barbituric acid	0.21	Plasma	[45]
5-Nonyl-5-ethyl barbituric acid	0.33	Plasma	[45]
Acebutolol	1.45	Plasma	[46]
Acrylic acid	0.23	Blood	[47]
AI-2 (SCH442416)	0.94	Blood	[48]
AI-6	0.58	Plasma	[48]
AI-9 (YH1885)	1.10	Plasma	[50]
Azithromycin	2.20	Serum	[51]
Alprazolam	1.02	Plasma	[52,72]
Alfentanil	0.00	Plasma	[57,72]
Azosemide	0.10	Plasma	[49]
Betaxolol	2.08	Plasma	[46]
Bisoprolol	1.36	Plasma	[46]
Bisphenol A (human)	0.16	Blood	[54]
Budesonide	0.94	Plasma	[53]
Cocaine	0.08	Plasma	[55,56]
Cefazolin	−0.10	Plasma	[57,72]
Chlordiazepoxide	0.69	Plasma	[72]
CDRI-81/470	−0.52	Serum	[58]
Daidzein	0.06	Blood	[54]
Daidzein (human)	0.08	Blood	[54]
Diazepam	0.65	Plasma	[72]
Dicloxacillin	−0.37	Plasma	[57]
Digoxin	1.18	Plasma	[72]
Dideoxyinosine (didanosine)	−0.12	Plasma	[72]
Doxorubicin	0.64	Plasma	[59]
Erythromycin	1.43	Serum	[51]
Fentanyl	0.58	Plasma	[46,57]
Flunitrazepam	0.57	Plasma	[72]
Fluoromisonidazole	0.28	Blood	[42]
Fluoxetine	0.77	Plasma	[60]
Ftorafur	−0.41	Plasma	[72]
Hexobarbital	0.78	Plasma	[57]
Hydroquinone	−0.12	Blood	[61]
Hydroxyzine	0.70	Blood	[62]
Imipramine	1.71	Plasma	[46]
Lidocaine	1.06	Plasma	[46]
Lorazepam	1.08	Plasma	[63]
Methotrexate	0.48	Plasma	[64]
Methylphenidate	0.65	Plasma	[65]
Metoprolol	1.63	Plasma	[46]
Midazolam	0.77	Plasma	[57,66,67]
Midazolam	0.57	Blood	[67]
Morphine	0.08	Plasma	[57]
Nalidixic acid	−0.23	Plasma	[57,72]
Nicotine	0.54	Plasma	[46]
Olanzapine	1.33	Plasma	[68]
Oxprenolol	1.02	Plasma	[46]
Pentazocine	0.37	Plasma	[46,57]
Penicillin V	−0.60	Plasma	[57,72]
5-Ethyl-5-phenylbarbital	0.26	Plasma	[57,72]
Phencyclidine	0.91	Plasma	[46]
Phenytoin	0.36	Plasma	[57,72]
p-Phenylbenzoic acid	−0.46	Plasma	[57]
Pindolol	1.04	Plasma	[46]
Procainamide	0.51	Plasma	[46,57]
Propranolol	0.75	Plasma	[46]
Pyrene	0.37	Plasma	[69]
Quinidine	1.22	Plasma	[46]
Salicylic acid	−0.64	Plasma	[57,72]
Timolol	0.95	Plasma	[46]
R-Etodolac	−0.92	Plasma	[57]
S-Etodolac	−0.37	Plasma	[57]
R-Carvedilol	0.65	Plasma	[46,57]
S-Carvedilol	1.07	Plasma	[46,57]
Terbinafine	0.18	Plasma	[70]
Thiopental (thiopentone)	0.36	Plasma	[57]
Thioridazine	0.94	Plasma	[60]
Triazolam	0.57	Plasma	[72]
Verapamil	0.72	Plasma	[71]
Valproic acid	0.26	Plasma	[57]

[a] All values for distribution to rat liver, except where indicated as human in column 1.

almost no cross-correlation of the descriptors in Eq. (6); the maximum correlation is $R^2 = 0.11$ between S and B. The predictive capability of Eq. (6) can be ascertained by dividing the 124 compounds into a test set and a training set. To make sure that the chemical space of the two sets is the same, we selected the sets using the Kennard and Stone method [41]. The training set yielded the equation,

$$\begin{aligned}\text{Log } K_{liver}(\text{human/rat}) = &-0.910(0.095) + 0.865(0.151)S \\ &+ 2.661(0.410)A + 2.125(0.222)B \\ &+ 0.553(0.029)L\end{aligned}$$

$$N = 62,\ R^2 = 0.923,\ R^2_{CV} = 0.917,\ \text{SD} = 0.280,\ F = 170.3 \quad (7)$$

When Eq. (7) was used to predict the independent test set of 62 compounds, comparison of the predicted and experimental values gave AE = 0.029, AAE = 0.190, RMSE = 0.234 and SD = 0.238 log units. There is therefore no bias in the predictions, with AE = 0.029, and Eq. (7), and by implication Eq. (6) can be used to predict further values of log K_{liver}(human) or

Table 3
SMILES nomenclature for some compounds

Solute	SMILES
AI-2 (SCH442416)	COc5ccc(CCCn1ncc2c1nc(N)n3nc(nc23)c4ccco4)cc5
AI-6	Nc1cc(Cl)c(cc1c2nnn[nH]2)S(N)(=O)=O
AI-9 (YH1885)	CC1N(CCc2ccccc12)c4nc(Nc3ccc(F)cc3)nc(C)c4C
CDRI-81/470	c1cc(ncc1)N2CCN(CC2)C(=O)c3cc4c(cc3)nc(n4)NC(OC)=O
JP-10	C3CC2C1CCC(C1)C2C3

log K_{liver}(rat) to around 0.26 log unit. This compares favourably with the only other assessment of predictive capability, that of Katritzky et al. [28]. It should be noted that predictions should only be made for compounds with descriptors within the range of those listed in Table 1. There were three outliers to Eq. (6), all of them for log K_{liver}(rat): methanol, obs 3.49 [1], calc 2.45 log units; ethanol obs 3.24 [1], calc 2.39 log units; allyl chloride obs 1.59 [1,3], calc 0.83 log units. There is nothing extraordinary about the three compounds, and we have no explanation for this behaviour.

3.2. Blood to liver distribution

Application of Eq. (5) to the *in vitro* values in Table 1 yielded Eq. (8),

$$\begin{aligned}\text{Log } P_{liver}(\text{human/rat})\ \textit{in vitro} = &-0.095(0.081)\\ &-0.366(0.090)S\\ &-0.357(0.230)A\\ &-0.180(0.113)B\\ &+0.730(0.076)V\end{aligned}$$

$$N = 125,\ R^2 = 0.583,\ R^2_{CV} = 0.569,\ \text{SD} = 0.228,\ F = 41.9 \quad (8)$$

The R^2 value is rather poor in Eq. (8), but the SD value of only 0.228 log units suggest that Eq. (8) could be used to predict further *in vitro* values of log P_{liver}(human/rat). In order to assess the predictive power of Eq. (8), we selected a training set of 62 VOCs by the Kennard and Stone method [41]. The training equation is as shown in Eq. (9),

$$\begin{aligned}\text{Log } P_{liver}(\text{human/rat})\ \textit{in vitro} = &\ 0.018(0.106)\\ &-0.469(0.130)S\\ &-0.273(0.346)A\\ &-0.191(0.057)B\\ &+0.651(0.107)V\end{aligned}$$

$$N = 62,\ R^2 = 0.515,\ R^2_{CV} = 0.481,\ \text{SD} = 0.240,\ F = 15.2 \quad (9)$$

The training equation, Eq. (9) was then used to predict log P_{liver}(human/rat) for the 63 compounds in the test set. Comparison of the predicted and experimental values gave AE = 0.020, AAE = 0.170, RMSE = 0.221 and SD = 0.223 log units. There is no bias in the predictions, and Eq. (9) and by implication the full Eq. (8) can therefore be used to predict values of log P_{liver}(human/rat) *in vitro* to 0.23 log units. The poor R^2 value for Eq. (8), especially by comparison to the R^2 value of 0.927 for Eq. (6), is due, at least in part, to the small spread of data in log P_{liver}(human/rat) *in vitro*, 2.73 log units, whereas for log K_{liver}(human/rat) the spread is 4.38 log units, see Table 1. The statistics of Eq. (8), R^2 and SD, are much inferior to those obtained previously by Abraham and Weathersby [4], Balaz and Luckacova [29], and by Zhang [30]. However, these authors used very small data sets of 28 or 29 VOCs, and several adjustable parameters.

The log P_{liver}(human/rat) values for the 85 drugs in Table 2 are all *in vivo* values. Application of Eq. (5) yielded Eq. (10); the $e \cdot E$ term was statistically not significant and was left out.

$$\begin{aligned}\text{Log } P_{liver}(\text{human/rat})\ \textit{in vivo} = &\ 0.292(0.149) - 0.296(0.093)S\\ &-0.334(0.154)A\\ &+0.181(0.121)B\\ &+0.337(0.114)V\\ &-0.597(0.153)\text{Ia}\end{aligned}$$

$$N = 85,\ R^2 = 0.522,\ R^2_{CV} = 0.441,\ \text{SD} = 0.420,\ F = 17.3 \quad (10)$$

The additional descriptor, Ia, is one we have used before [36] and takes the value Ia = 1 for carboxylic acids and Ia = 0 for all other compounds. We divided the 85 compounds into a training set and a test set. For the training set we obtained Eq. (11),

$$\begin{aligned}\text{Log } P_{liver}(\text{human/rat})\ \textit{in vivo} = &\ 0.344(0.212) - 0.305(0.111)S\\ &-0.508(0.235)A\\ &+0.304(0.162)B\\ &+0.289(0.146)V\\ &-0.511(0.211)\text{Ia}\end{aligned}$$

$$N = 43,\ R^2 = 0.598,\ R^2_{CV} = 0.427,\ \text{SD} = 0.415,\ F = 11.0 \quad (11)$$

Then Eq. (11) was used to predict log P_{liver} for the remaining 42 compounds in the test set. For the observed and predicted values we find AE = 0.093, AAE = 0.304, RMSE = 0.438 and SD = 0.443 log units. Hence there is only a small bias in the predictions, with AE = 0.093 log units. The AAE = 0.304 and the SD = 0.443 log units indicate that Eq. (11) and hence the full Eq. (10) can predict log P_{liver}(human/rat) *in vivo* to about 0.45 log units (SD). This is better than the general equations of Zhang and Zhang [31] that lead to SD = 0.55 log units for a rather small test set.

We also investigated the possibility of combining the *in vitro* and *in vivo* values in Tables 1 and 2. We used the descriptors in Eq. (5) plus an indicator variable for the *in vitro* and *in vivo* values; Iv takes the value 1.0 for the *in vitro* values and 0.0 for the *in vivo* values. The resulting equation is,

$$\begin{aligned}&\text{Log } P_{liver}(\text{human/rat})\ \textit{in vitro}\ \text{and}\ \textit{in vivo}\\ &\quad = 0.147(0.097) - 0.354(0.055)S - 0.260(0.100)A\\ &\qquad +0.553(0.047)V - 0.579(0.115)\text{Ia} - 0.139(0.079)\text{Iv}\end{aligned}$$

$$N = 210,\ R^2 = 0.544,\ R^2_{CV} = 0.502,\ \text{SD} = 0.324,\ F = 48.8 \quad (12)$$

The Iv descriptor in Eq. (12) is just significant (−0.139, SD = 0.079 log units, $T = -1.75$, $p = 0.082$). The 210 compounds were divided into a training set and a test set. For the training set the following regression equation was obtained,

$$\begin{aligned}&\text{Log } P_{\text{liver}}(\text{human/rat}) \textit{ in vitro} \text{ and } \textit{in vivo}\\ &= 0.123(0.139) - 0.293(0.072)S - 0.387(0.150)A\\ &\quad + 0.550(0.060)V - 0.494(0.157)\text{Ia} - 0.113(0.116)\text{Iv}\\ &N = 105,\ R^2 = 0.592,\ R^2_{\text{CV}} = 0.501,\ \text{SD} = 0.318,\ F = 28.8\end{aligned} \quad (13)$$

When Eq. (13) was used to predict the 105 compounds test set, the predictions and observation had AE = 0.055, AAE = 0.248, RMSE = 0.335 and SD = 0.337 log units. Thus Eq. (13) and hence Eq. (12) can be used to predict further values with little bias in the predictions, and with a SD = 0.34 log units. The statistics of the test set for Eq. (12) are a little better than those of the test set for Eq. (10), and we suggest that Eq. (12) can be used to predict further values of log P_{liver} for drugs. Prediction of log P_{liver} for VOCs is best carried out through Eq. (8).

Rodgers et al. [46] have correlated partition of drugs from plasma water to various tissues, including liver, as Kpu. They give observed and calculated values on their Eqs. (19) and (20) [46]. We have transformed the values into log Kpu in order to be comparable with our results and find for partition to liver that for 26 drugs their best equation, Eq. (19) [43] yields SD = 0.372 log units. This is better than our SD = 0.420 log units for 85 drugs in Eq. (10) but not as good as our SD = 0.324 log units for 210 drugs and VOCs in Eq. (12). Poulin and Theil [33] have predicted various plasma to tissue partition coefficients in their physiologically based pharmacokinetics model of drug disposition. As input, knowledge of the partition coefficients from water to octanol and water to olive oil of a given drug is required. They give predictions of log P_{liver} for three particular drugs [32], and a comparison of their predictions with predictions and fits based on Eqs. (10) and (12) is given in Table 4. There is good agreement between the two, very different, methods.

The statistics of our equations for partition to brain [35,36], to muscle [37], and to fat [38] are much better than for partition to liver. This is not surprising in view of the extent to which metabolism takes place in the liver. The latter phenomenon suggests that our SD values of 0.228 log units for Eq. (8) and 0.324 log units for Eq. (12) are reasonable errors for predictive purposes.

4. Conclusions

A large data set of 124 air to liver *in vitro* partition coefficients for VOCs can be correlated through an Abraham solvation equation. Division into training and test sets indicated that the equation can be used to predict further values with AE = 0.03 and SD = 0.24 log units. It was not necessary to separate air to rat liver and air to human liver partition coefficients; the 114 values include both partitions. Blood to liver *in vitro* partition coefficients for VOCs (125 data points) can again be correlated through an Abraham solvation equation. Although the R^2 value is not very good, an assessment of predictive capability suggests the equation can be used to predict further values with AE = 0.02 and SD = 0.22 log units.

Table 4
Predicted values of *in vivo* log P_{liver} by Poulin and Theil [32], and fitted and predicted values in this work

Compound	Poulin and Theil	This work	
		Eq. (12)	Eq. (10)
Diazepam	0.70	0.75[a]	0.76[a]
Propranolol	0.75	0.71[a]	0.68[a]
2-Ethoxybenzamide	−0.13	0.21	0.27

[a] These are fitted values.

The 85 *in vivo* values of blood/plasma/serum to liver partition coefficients for drugs yielded a correlation equation that could be used to predict further values with AE = 0.09 and SD = 0.44 log units, but a rather better equation could be constructed through a combination of the *in vitro* and *in vivo* values for blood/plasma/serum to liver partition coefficients (210 data points). Training and test sets indicated that this combined equation could be used to predict further values with AE = 0.05 and SD = 0.34 log units; it is this equation that we recommend for predictions for drug molecules.

As usual, predictions should only be made for compounds within (or perhaps slightly beyond) the chemical space of the compounds used to set up the correlation equations. In the present work, this chemical space is defined by the range of the Abraham descriptors used in the equations. Provided that partition takes place by passive transport, predictions can be made for any compound with descriptors within this range. Unlike predictions based on functional group analysis, it is not necessary to have compounds of similar chemical structure in the training set.

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