Air to Blood Distribution of Volatile Organic Compounds: A Linear Free Energy Analysis

Michael H. Abraham,*,† Adam Ibrahim,† and William E. Acree, Jr.‡

Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, United Kingdom, and Department of Chemistry, University of North Texas, P.O. Box 305070, Denton, Texas 76203-5070

Received March 3, 2005

Partition coefficients, K_{blood}, for volatile organic compounds from air to blood have been collected for 155 compounds (air to human blood) and 127 compounds (air to rat blood). For 86 common compounds, the average error, AE, between the two sets of log K_{blood} values is 0.12 log units, somewhat smaller than our estimated interlaboratory average SD value of around 0.16 log units. We conclude that with regard to experimental errors, there is no significant difference between K_{blood} values in human blood and in rat blood. There are 196 compounds for which either or both K_{blood} (human) and K_{blood} (rat) are available. A training set of 98 compounds could be fitted with the Abraham solvation parameters with $R^2 = 0.933$ and SD = 0.34 log units. The training equation was then used to predict the test set of values with AE = 0.04 log units, SD = 0.33 log units, and an average absolute error, AAE, of 0.25 log units. A second training and test set yielded similar values: AE = 0.01, SD = 0.39, and AAE = 0.29 log units. It is concluded that it is possible to construct an equation capable of predicting further values of log K_{blood} to around 0.30 log units. Because the descriptors used in the correlation equations can be predicted from structure, it is now possible to predict log K_{blood} for any chemical structure.

Introduction

The distribution of volatile organic compounds (VOCs) between air and blood is of particular interest to environmentalists and toxicologists, as evidenced by the large body of data that has been gathered (*1−41*). Reported data are usually presented as the air to blood partition coefficient at 37 °C, K_{blood}, or log K_{blood}, as in eq 1

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

Concentrations are expressed as mol L^{-1} in blood and in air, so that K_{blood} has no units and is equivalent to the Ostwald solubility coefficient. Nearly all of the available data refers to either human blood or rat blood. Quite often, these are taken as equivalent. Gargas et al. (*6*), however, investigated in some detail possible differences between air to human blood and air to rat blood distribution for a group of VOCs, which included 36 common compounds. They obtained the regression shown as eq 2, where the standard deviation (SD) of the coefficients is given in parentheses. The number of data points (compounds) is N, the correlation coefficient is R, and the root-mean-square error is RMSE. Because of the intercept of −0.23 log units, Gargas et al. (*6*) concluded that log K_{blood} (human) was not the same as log K_{blood} (rat) and that in general K_{blood} (rat) was larger than K_{blood} (human) by a factors of 1.5−2.0.

$$\log K_{blood}\,(\text{human}) = -0.23\,(0.051) + 1.01\,(0.037)\log K_{blood}\,(\text{rat}) \quad (2)$$

where $N = 36$, $R^2 = 0.96$, and RMSE = 0.132.

This is a very important conclusion because, if correct, it would imply that correlations and predictions of air to blood distribution have to be carried out separately for the two species. However, the analysis of Gargas et al. (*6*) does not seem to take into account the error in the experimental values of K_{blood}. Meulenberg and Vijverberg (*7*) found ratios between 1.3 and 1.7, depending on the data set. Kaneko et al. (*39*) measured K_{blood} (human) and K_{blood} (rat) for eight esters and eight alcohols and found smaller ratios of 1.08 for the esters and 1.44 for the alcohols. The first aim of this work is to investigate any difference between log K_{blood} (human) and log K_{blood} (rat) for an extended data set and with due regard to experimental errors.

The second aim is to attempt to obtain correlation equations that can be used for the prediction of further values of log K_{blood}, taking human and rat data either separately or together. There have been comparatively few correlative analyses of log K_{blood} and even fewer analyses that assess the predictive power of any correlation equations. To carry out such an assessment, it is necessary to divide the total data set into a training set and a test set. The former set is used to construct a correlation equation that is then used to predict values for the independent test set. In Table 1 are listed summaries of the statistics of correlation equations for log K_{blood}. It should be noted that values of log K_{blood} that have been calculated through an equation applied to a training set are often described as "predicted" values.

* To whom correspondence should be addressed. E-mail: m.h.abraham@ucl.ac.uk.
† University College London.
‡ University of North Texas.

10.1021/tx050066d CCC: $30.25
Published on Web 04/23/2005

Table 1. Statistics for the Correlation and Prediction of Log K_{blood}

	training set				test set			
ref	*a*	*N*	R^2	SD	*N*	SD	AAE	AE
1	H	82	0.98	0.20				
6	H	55	0.93	0.18				
37[b]	H	20	0.93	0.16				
7	H	109	0.99					
7	R	92	0.93					
42	R				45	0.58	0.47	0.47
c	H	155	0.94	0.344				
c	R	127	0.91	0.29				
c	R + H	98	0.93	0.34	98	0.33	0.26	0.04
c	R + H	196	0.94	0.32				
c	S	282	0.93	0.33				

[a] H, human blood; R, rat blood. [b] Chlorinated hydrocarbons only. [c] This work. H + R indicates human and rat data averaged, and S indicates human and rat data taken separately. In the latter case, *N* is the number of data points; the number of compounds is 196.

This is not correct, and we make a firm distinction between calculated values from a training equation and predicted values for a test set that has not been used to construct the training equation. In the event, there appears to be no case of an analysis using training sets and test sets. Poulin and Krishnan (*42*) used an equation based on solubilities of compounds in saline and vegetable oil to calculate log K_{blood} (rat) as true predictions, equivalent to a test set. In Table 1 are the statistics for the predictions that we have calculated for the entire set of 45 compounds used by Poulin and Krishnan (*42*).

Materials and Methods

Our general method for the correlation and prediction of log K_{blood} values is based (*43*, *44*) on the solvation equation, or linear free energy relationship (LFER), eq 3. In this equation, the dependent variable, SP, is log K_{blood}, and the independent variables are compound descriptors as follows (*43*, *44*): 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, and L is the logarithm of the gas−hexadecane partition coefficient at 25 °C. The coefficients in eq 3 are evaluated through multiple linear regression analysis.

$$\mathrm{SP} = \mathrm{c} + \mathrm{e.\ E} + \mathrm{s.\ S} + \mathrm{a.\ A} + \mathrm{b.\ B} + \mathrm{l.\ L} \qquad (3)$$

The compound descriptors in eq 3 are available for some 3000 compounds and can be predicted just from structure, if required (*45*). Application to the correlation of log K_{blood} values is straightforward; the log K_{blood} values are regressed against the set of descriptors in a multiple linear regression analysis. The compounds that we have studied and the log K_{blood} values are collected in Table 2.

Results and Discussion

Comparison of Data on Human and Rat Blood. We have a total of 86 compounds for which both log K_{blood} (human) and log K_{blood} (rat) are available, considerably more than any previous comparison. Following Gargas et al. (*6*), we obtained eq 4

$$\log K_{blood}\ (\text{human}) = -0.12\ (0.047) + 1.00\ (0.028) \log K_{blood}\ (\text{rat}) \qquad (4)$$

where $N = 86$, $R^2 = 0.94$, RMSE = 0.279, and SD = 0.280. Plotting log K_{blood} (human) against log K_{blood} (rat) is actually not the most appropriate method to compare the two sets of data. It is simpler, and better, to obtain statistics on the two sets of data. These are in Table 3; AE is the average error (rat−human) and AAE is the average absolute error. The statistics AAE, SD, and RMSE all describe the same effect, that is, random errors; it is only the AE that indicates any bias in the two sets of data. We can conclude from AE = 0.124 log units that the ratio between K_{blood} (rat) and K_{blood} (human) is about 1.3, that is, less than the ratio found by Gargas et al. (*6*) and near the ratios found by Poulin and Krishnan (*42*).

As we have suggested, comparisons between log K_{blood} (human) and log K_{blood} (rat) have very little meaning without consideration of the experimental error of the measurements. Fiserova-Bergerova et al. (*5*) were one of the first investigators to report large discrepancies in air to blood partitions. They found that their values for gas to blood partitions for propanone and butanone appeared different from those of other investigators using methods based on the same experimental principle. They had no explanation for the discrepancies and suggested that it was possibly experimental error in the measurements.

There are not many compounds for which enough repeat measurements in different laboratories have been carried out to obtain a SD value. We have found enough data for three VOCs, however, as shown in Table 4. The three SD values for log K_{blood} (human) are 0.34 (propanone), 0.09 (chloroform), and 0.06 (trichloroethene), with an average of 0.16 log units. We further note that in reporting air to blood partitioning data, several authors estimated the uncertainty in their measured values based on replicate measurements. In some instances (*14*, *29*, *40*, *41*), the estimated uncertainties exceeded 0.09 log units. These uncertainties are "within laboratory" errors and will be less than interlaboratory errors. They are therefore in line with our estimate of interlaboratory SD values of 0.16 log units. On the basis of the above observations, we think it is reasonably clear that the experimental error in general will be larger (certainly not smaller) than the systematic bias between log K_{blood} (human) and log K_{blood} (rat), which we find is 0.124 log units over 86 compounds. Thus, the bias of 0.124 log units is smaller than experimental error and is statistically not significant. This is a very important result, because it means that data on log K_{blood} (human) and log K_{blood} (rat) can be combined in any correlative analysis.

Correlation and Prediction of Log K_{blood} for Humans and Rats. In Table 2 are listed values of log K_{blood} (human) for 155 VOCs and values of log K_{blood} (rat) for 127 VOCs. We first correlate these separately against our descriptors, according to eq 3, and obtain

$$\log K_{blood}\ (\text{human}) = -1.18 + 0.39\ \mathrm{E} + 0.97\ \mathrm{S} + 3.80\ \mathrm{A} + 2.69\ \mathrm{B} + 0.41\ \mathrm{L} \qquad (5)$$

where $N = 155$, $R^2 = 0.94$, SD = 0.34, RMSE = 0.332, and $F = 474$, and

$$\log K_{blood}\ (\text{rat}) = -0.75 + 0.56\ \mathrm{E} + 1.06\ \mathrm{S} + 3.64\ \mathrm{A} + 2.41\ \mathrm{B} + 0.29\ \mathrm{L} \qquad (6)$$

where $N = 127$, $R^2 = 0.91$, SD = 0.29, RMSE = 0.286,

Table 2. Compound Descriptors and Log *K* Values for Air to Blood Partition

solute	E	S	A	B	L	human log *K*	human ref	rat log *K*	rat ref	average log *K*
1,1,1,2-tetrachloroethane	0.542	0.630	0.100	0.080	3.641	1.48	*1, 6, 7*	1.62	*6, 7*	1.55
1,1,1-trichloroethane	0.369	0.410	0.000	0.090	2.733	0.50	*1, 4−7*	0.76	*6, 7*	0.63
1,1,2,2-tetrachloroethane	0.595	0.760	0.160	0.120	3.803	2.11	*1, 4, 6, 7*	2.15	*6, 7*	2.13
1,1,2-trichloroethane	0.499	0.680	0.130	0.130	3.290	1.58	*1, 4, 6, 7*	1.76	*6, 7*	1.67
1,1-dichloroethane	0.322	0.490	0.100	0.100	2.316	0.70	*1, 4, 6, 7*	1.05	*6, 7*	0.88
1,2,4-trimethylbenzene	0.677	0.560	0.000	0.190	4.441	1.77	*7*	1.16	*16, 17*	1.47
1,2-dichloroethane	0.416	0.640	0.100	0.110	2.573	1.30	*1, 4, 6, 7*	1.48	*6, 7*	1.39
1,2-dichloropropane	0.371	0.680	0.000	0.150	2.866	1.01	*1, 4, 6, 7*	1.27	*6, 7*	1.14
1-bromo-2-chloroethane	0.572	0.700	0.100	0.090	2.982	1.47	*6, 7*	1.72	*6, 7*	1.60
1-butanol	0.224	0.420	0.370	0.480	2.601	2.97	*4, 7*	3.19	*7*	3.08
1-chloropropane	0.216	0.400	0.000	0.100	2.202	0.46	*1, 6, 7*	0.72	*6, 7*	0.59
1-nitropropane	0.240	0.950	0.000	0.310	2.894	2.27	*6, 7*	2.35	*6, 7*	2.31
1-pentanol	0.219	0.420	0.370	0.480	3.106	2.73	*7*	2.92	*7*	2.83
1-propanol	0.236	0.420	0.370	0.480	2.031	2.99	*1, 5, 7*	3.13	*7*	3.06
2,2,4-trimethylpentane	0.000	0.000	0.000	0.000	3.106	0.20	*6, 7*	0.25	*6, 7*	0.23
2-chloropropane	0.177	0.350	0.000	0.120	1.970	0.14	*6, 7*	0.49	*6, 7*	0.32
2-heptanone	0.123	0.680	0.000	0.510	3.760	2.30	*1, 7*	2.35	*7*	2.33
2-methyl-1,3-butadiene	0.313	0.230	0.000	0.100	2.101	−0.12	*2*	0.32	*2, 6, 7*	0.10
2-methyl-1-propanol	0.217	0.390	0.370	0.480	2.413	2.89	*1, 4, 5, 7*	2.94	*7*	2.92
2-nitropropane	0.216	0.920	0.000	0.330	2.550	2.19	*6, 7*	2.26	*6, 7*	2.23
2-pentanone	0.143	0.680	0.000	0.510	2.755	2.18	*1*	2.10	*7*	2.14
2-propanol	0.212	0.360	0.330	0.560	1.764	2.92	*1, 4, 5, 7*	3.11	*7*	3.02
3-methyl-1-butanol	0.192	0.390	0.370	0.480	3.011	2.58	*7*	2.92	*7, 22*	2.75
4-chlorobenzotrifluoride	0.530	0.580	0.000	0.010	3.730	1.22	*10*	1.64	*10*	1.43
4-methyl-2-pentanone	0.111	0.650	0.000	0.510	3.089	2.01	*1, 4, 7*	1.90	*7*	1.96
propanone	0.179	0.700	0.040	0.490	1.696	2.35	*1, 4, 5, 7*	2.37	*7, 22*	2.36
benzene	0.610	0.520	0.000	0.140	2.786	0.87	*1, 5−7*	1.22	*6, 7, 17*	1.05
tetrachloromethane	0.458	0.380	0.000	0.000	2.823	0.57	*1, 4, 6, 7*	0.66	*6, 7*	0.62
bromochloromethane	0.541	0.800	0.010	0.060	2.445	0.79	*4*	1.62	*6, 7*	1.21
bromodichloromethane	0.593	0.690	0.100	0.040	2.891	1.42	*32*	1.56	*31, 33*	1.49
butyl acetate	0.071	0.600	0.000	0.450	3.353	1.92	*7*	1.95	*7*	1.94
butan-2-one	0.166	0.700	0.000	0.510	2.287	2.19	*1, 4, 5, 7*	2.28	*7*	2.24
halothane	0.102	0.380	0.150	0.050	2.177	0.40	*1, 5, 7*	0.73	*7, 12*	0.57
1-chloro-2,2,2-trifluoroethane	0.010	0.400	0.150	0.000	1.168	0.18	*1, 5, 7*	0.10	*6, 7*	0.14
enflurane	−0.230	0.400	0.120	0.130	1.750	0.25	*1, 5, 7, 26*	0.45	*26*	0.35
isoflurane	−0.240	0.500	0.100	0.100	1.576	0.15	*1, 5, 7*	0.25	*6, 7*	0.20
chlorobenzene	0.718	0.650	0.000	0.070	3.657	1.48	*1, 6, 7*	1.77	*6, 7*	1.63
chlorodibromomethane	0.775	0.710	0.070	0.080	3.304	1.71	*6, 7, 32*	2.04	*6, 7, 31*	1.88
chloroethane	0.227	0.400	0.000	0.100	1.678	0.36	*1, 6, 7*	0.61	*6, 7*	0.49
trichloromethane	0.425	0.490	0.150	0.020	2.480	0.98	*1, 4−7, 32*	1.32	*7, 31*	1.15
cis-1,2-dichloroethene	0.436	0.610	0.110	0.050	2.439	0.98	*1, 6, 7*	1.33	*6, 7*	1.16
cyclohexane	0.305	0.100	0.000	0.000	2.964	0.19	*1, 4−6*	0.14	*6, 7*	0.17
cyclopropane	0.408	0.230	0.000	0.000	1.314	−0.29	*1, 5, 7, 26*	−0.12	*26*	−0.21
decane	0.000	0.000	0.000	0.000	4.686	1.92	*4*	1.02	*7, 17*	1.47
dichloromethane	0.387	0.570	0.100	0.050	2.019	0.95	*1, 4−7*	1.29	*6, 7*	1.12
diethyl ether	0.041	0.250	0.000	0.450	2.015	1.09	*1, 5, 7, 26*	1.12	*7, 26*	1.11
ethane	0.000	0.000	0.000	0.000	0.492	−1.07	*1, 26*	−0.97	*7, 26*	−1.02
ethanol	0.246	0.420	0.370	0.480	1.485	3.17	*1, 4, 5, 7*	3.37	*7*	3.27
ethene	0.107	0.100	0.000	0.070	0.289	−0.75	*1, 7, 29*	−0.31	*29*	−0.53
ethyl acetate	0.106	0.620	0.000	0.450	2.314	1.91	*4, 7*	1.89	*7, 22*	1.90
ethylbenzene	0.613	0.510	0.000	0.150	3.778	1.45	*1, 4, 7*	1.48	*7*	1.47
ethylene oxide	0.250	0.740	0.070	0.320	1.371	1.79	*29*	1.81	*23*	1.80
heptane	0.000	0.000	0.000	0.000	3.173	0.42	*1, 4−7*	0.58	*6, 7, 17*	0.50
hexachloroethane	0.680	0.680	0.000	0.000	4.718	1.72	*6, 7*	1.80	*6, 7*	1.76
hexane	0.000	0.000	0.000	0.000	2.668	0.07	*1, 4, 5, 7*	0.35	*6, 7, 17*	0.21
isobutyl acetate	0.052	0.570	0.000	0.470	3.161	1.65	*7*	1.72	*7*	1.69
isopentyl acetate	0.051	0.570	0.000	0.470	3.740	1.77	*7*	1.81	*7*	1.79
isopropyl acetate	0.055	0.570	0.000	0.470	2.546	1.54	*4, 7*	1.55	*7*	1.55
2-brompropane	0.332	0.350	0.000	0.140	2.390	0.41	*6, 7*	0.86	*6−8*	0.64
JP-10	0.590	0.450	0.000	0.060	4.840	1.72	*6*	1.79	*6*	1.76
methoxyflurane	0.109	0.670	0.070	0.140	2.864	1.16	*1, 5, 7*	1.40	*7*	1.28
methanol	0.278	0.440	0.430	0.470	0.970	3.29	*1, 4, 5, 7*	3.52	*7*	3.41
methyl acetate	0.142	0.640	0.000	0.450	1.911	1.95	*7*	2.00	*7*	1.98
methyl *tert*-butyl ether	0.024	0.210	0.000	0.590	2.380	1.25	*7, 19*	1.11	*11, 19*	1.18
chloromethane	0.249	0.430	0.000	0.080	1.163	0.23	*1, 6, 7*	0.39	*6, 7*	0.31
methylcyclohexane	0.244	0.060	0.000	0.000	3.319	0.61	*4*	0.79	*17*	0.70
1,3-dimethylbenzene	0.623	0.520	0.000	0.160	3.839	1.51	*1, 4, 6, 7*	1.66	*6, 7*	1.59
nonane	0.000	0.000	0.000	0.000	4.182	1.70	*4*	0.63	*16, 17*	1.17
octane	0.000	0.000	0.000	0.000	3.677	0.61	*4*	0.74	*7, 17*	0.68
o-xylene	0.663	0.560	0.000	0.160	3.939	1.53	*1, 7*	1.30	*7, 17*	1.42
pentyl acetate	0.067	0.600	0.000	0.450	3.844	1.97	*7*	1.99	*7*	1.98
propene	0.103	0.080	0.000	0.070	0.946	−0.36	*3*	−0.06	*3*	−0.21
propyl acetate	0.092	0.600	0.000	0.450	2.819	1.87	*7*	1.88	*7*	1.88
1-bromopropane	0.366	0.400	0.000	0.120	2.620	0.85	*6, 7*	1.09	*6−8*	0.97
p-xylene	0.613	0.520	0.000	0.160	3.839	1.60	*1, 4, 6, 7*	1.62	*6, 7*	1.61

Table 2 (Continued)

						human		rat		average
solute	E	S	A	B	L	log *K*	ref	log *K*	ref	log *K*
styrene	0.849	0.650	0.000	0.160	3.856	1.73	*1, 4, 7*	1.60	*6, 7*	1.67
sulfur hexafluoride	−0.600	−0.200	0.000	0.000	−0.120	−2.22	*1, 26*	−2.12	*26*	−2.17
2-methyl-2-propanol	0.180	0.300	0.310	0.600	1.963	2.66	*7, 19*	2.70	*11, 19*	2.68
tert-amyl methyl ether	0.050	0.210	0.000	0.600	2.916	1.25	*19*	1.19	*19*	1.22
tetrachloroethene	0.639	0.440	0.000	0.000	3.584	1.09	*1, 4, 6, 7*	1.28	*6, 7*	1.19
toluene	0.601	0.520	0.000	0.140	3.325	1.12	*1, 4, 5*	1.16	*6, 7, 17*	1.14
trans-1,2-dichloroethene	0.425	0.410	0.090	0.050	2.278	0.77	*1, 6, 7*	0.98	*6, 7*	0.88
tribromomethane	0.974	0.680	0.150	0.060	3.784	2.02	*4, 32*	2.27	*31*	2.15
trichloroethene	0.524	0.370	0.080	0.030	2.997	0.94	*1, 4−7*	1.33	*6, 7, 27, 28*	1.14
vinyl bromide	0.564	0.500	0.000	0.070	1.846	0.36	*6, 7*	0.61	*6, 7*	0.49
vinyl chloride	0.258	0.380	0.000	0.050	1.404	0.06	*6, 7, 30*	0.27	*6, 7, 27, 30*	0.17
propylbenzene	0.604	0.500	0.000	0.150	4.230	1.67	*1, 7*			1.67
sevoflurane	−0.465	0.232	0.080	0.147	1.688	−0.20	*1, 5, 7*			−0.20
1,2,3-trichloropropane	0.547	0.650	0.020	0.330	3.566	2.01	*4*			2.01
1,2,3-trimethylbenzene	0.728	0.610	0.000	0.190	4.565	1.82	*7*			1.82
1,2-dichlorobenzene	0.872	0.780	0.000	0.040	4.518	2.63	*1, 7*			2.63
1,3,5-trimethylbenzene	0.649	0.520	0.000	0.190	4.344	1.64	*4, 7*			1.64
1,3-butadiene	0.320	0.230	0.000	0.100	1.543	0.09	*21*			0.09
1,3-dichlorobenzene	0.847	0.730	0.000	0.020	4.410	2.30	*1, 7*			2.30
1-chlorobutane	0.210	0.400	0.000	0.100	2.722	0.63	*1, 7*			0.63
1-chloropentane	0.208	0.380	0.000	0.090	3.223	0.87	*1, 7*			0.87
1-fluoropropane	0.034	0.350	0.000	0.130	1.103	0.02	*1*			0.02
1-methoxy-2-propanol	0.218	0.610	0.350	0.620	2.655	4.09	*7, 20*			4.09
2,2-dimethylbutane	0.000	0.000	0.000	0.000	2.352	−0.59	*1, 5, 7*			−0.59
2,3-dimethylbutane	0.000	0.000	0.000	0.000	2.495	0.78	*4*			0.78
2-butoxyethanol	0.201	0.500	0.300	0.830	3.806	3.90	*7, 20*			3.90
2-ethoxyethanol	0.237	0.520	0.310	0.810	2.792	4.34	*7, 20*			4.34
2-fluoropropane	0.004	0.320	0.000	0.100	1.070	0.06	*1*			0.06
2-hexanone	0.136	0.680	0.000	0.510	3.286	2.10	*1*			2.10
2-isopropoxyethanol	0.196	0.470	0.300	0.910	3.170	4.16	*7, 20*			4.16
2-methoxyethanol	0.269	0.500	0.300	0.840	2.490	4.52	*7, 20*			4.52
2-methylcyclohexanone	0.372	0.830	0.000	0.560	4.055	2.87	*4*			2.87
2-methylpentane	0.000	0.000	0.000	0.000	2.503	−0.39	*1, 5, 7*			−0.39
3-methylhexane	0.000	0.000	0.000	0.000	3.044	0.11	*1, 5, 7*			0.11
3-methylpentane	0.000	0.000	0.000	0.000	2.581	−0.37	*1, 5, 7*			−0.37
3-pentanone	0.154	0.660	0.000	0.510	2.811	2.21	*1, 7*			2.21
acetylene	0.190	0.600	0.060	0.040	0.140	−0.06	*1*			−0.06
allylbenzene	0.717	0.600	0.000	0.220	4.136	1.71	*1, 7*			1.71
argon	0.000	0.000	0.000	0.000	−0.688	−1.52	*1*			−1.52
carbon disulfide	0.876	0.260	0.000	0.030	2.370	0.30	*1*			0.30
carbon monoxide	0.000	0.000	0.000	0.040	−0.836	−1.67	*1*			−1.67
1-chloro-2,2-difluoroethene	−0.340	0.290	0.150	0.000	0.723	0.06	*1, 5*			0.06
1,2-dichlorotetrafluoroethane	−0.190	0.050	0.000	0.000	1.427	−0.82	*1*			−0.82
1,1,2,2,3,3,4,4-octafluorobutane	−0.710	0.040	0.090	0.000	0.590	−0.36	*7*			−0.36
1,1,2,2,3-pentafluoropropane	−0.450	0.170	0.000	0.030	0.680	−0.48	*7*			−0.48
1,1,2,2-tetrafluoroethane	−0.280	−0.300	0.300	0.000	0.289	−0.12	*7*			−0.12
1,1,2,4,4-pentafluorobutane	−0.500	1.250	0.120	0.130	2.324	0.87	*7*			0.87
1,1-difluoroethane	−0.250	0.490	0.040	0.050	0.517	0.42	*7*			0.42
teflurane	−0.070	0.210	0.200	0.020	1.370	−0.22	*1, 7*			−0.22
1,1,1,2,2,3,3,4,4-nonafluorobutane	−0.780	−0.300	0.100	0.100	0.420	−1.52	*7*			−1.52
1,1,1,2-tetrafluoroethane	−0.640	0.200	0.240	0.000	0.226	−0.25	*7*			−0.25
1,1,1,2,3,4,4,4-octafluorobutane	−0.710	−0.090	0.090	0.040	0.590	−0.59	*7*			−0.59
fluroxene	0.183	0.300	0.000	0.270	1.600	0.15	*1, 5, 7*			0.15
tetrafluoromethane	−0.550	−0.200	0.000	0.000	−0.819	−1.10	*7*			−1.10
halopropane	−0.070	0.280	0.200	0.000	2.030	0.75	*1*			0.75
desflurane	−0.540	0.270	0.070	0.170	0.740	−0.37	*1*			−0.37
cyclohexanone	0.403	0.860	0.000	0.560	3.792	3.33	*4*			3.33
difluorodichloromethane	0.037	0.130	0.000	0.000	1.124	−0.82	*1*			−0.82
dimethyl ether	0.000	0.270	0.000	0.410	1.285	1.16	*1*			1.16
divinyl ether	0.259	0.390	0.000	0.130	1.760	0.41	*1, 5, 7*			0.41
ethyl formate	0.146	0.660	0.000	0.380	1.845	1.65	*1*			1.65
ethyl *tert*-butyl ether	−0.020	0.160	0.000	0.600	2.720	1.07	*7, 19*			1.07
ethyl tert-pentyl ether	0.030	0.230	0.000	0.370	3.200	1.25	*7*			1.25
fluoroethane	0.052	0.350	0.000	0.100	0.576	0.09	*1*			0.09
fluorotrichloromethane	0.207	0.240	0.000	0.070	1.950	−0.06	*1*			−0.06
helium	0.000	0.000	0.000	0.000	−1.741	−2.00	*1*			−2.00
hydrogen	0.000	0.000	0.000	0.000	−1.200	−1.77	*1*			−1.77
iodoethane	0.640	0.400	0.000	0.150	2.573	0.83	*1*			0.83
isophorone	0.511	1.120	0.000	0.530	4.740	3.37	*4*			3.37
isopropylbenzene	0.602	0.490	0.000	0.160	4.084	1.57	*1, 7*			1.57
krypton	0.000	0.000	0.000	0.000	−0.211	−1.22	*1*			−1.22
methane	0.000	0.000	0.000	0.000	−0.323	−1.42	*1*			−1.42
3-methylpentan-2-one	0.110	0.650	0.000	0.510	3.163	2.23	*7*			2.23
methylcyclopentane	0.225	0.100	0.000	0.000	2.907	−0.07	*1, 5, 7*			−0.07
neon	0.000	0.000	0.000	0.000	−1.575	−2.01	*1*			−2.01

Table 2 (Continued)

solute	E	S	A	B	L	human log K	human ref	rat log K	rat ref	average log K
nitrogen	0.000	0.000	0.000	0.000	−0.978	−1.83	*1*			−1.83
nitrous oxide	0.068	0.350	0.000	0.100	0.164	−0.34	*1, 5*			−0.34
oxygen	0.000	0.000	0.000	0.000	−0.723	−1.58	*1*			−1.58
pentane	0.000	0.000	0.000	0.000	2.162	−0.29	*1, 4, 5, 7*			−0.29
xenon	0.000	0.000	0.000	0.000	0.378	−0.85	*1, 5*			−0.85
1,1-dichloro-1-fluoroethane	0.084	0.430	0.010	0.050	1.920			0.32	*13*	0.32
1,1-dichloroethylene	0.362	0.340	0.000	0.050	2.110			0.70	*6, 7*	0.70
1,2,4-trifluorobenzene	0.410	0.650	0.000	0.020	2.850			0.76	*7*	0.76
1,2,4-trimethylcyclohexane	0.360	0.210	0.000	0.000	4.100			0.87	*16, 17*	0.87
1,2-dibromoethane	0.747	0.760	0.100	0.170	3.382			2.08	*6, 7*	2.08
1,2-difluorobenzene	0.390	0.630	0.000	0.060	2.843			0.96	*7*	0.96
1,2-dimethylcyclohexane	0.320	0.230	0.000	0.000	3.800			0.91	*17*	0.91
1,2-epoxy-3-butene	0.370	0.470	0.000	0.360	2.257			1.97	*24*	1.97
1,3,5-trifluorobenzene	0.390	0.490	0.000	0.000	2.660			0.49	*7*	0.49
1,4-difluorobenzene	0.384	0.600	0.000	0.060	2.766			0.87	*7*	0.87
1-decene	0.093	0.080	0.000	0.070	4.533			1.21	*18*	1.21
1-hexanol	0.210	0.420	0.370	0.480	3.610			3.21	*7*	3.21
1-nonene	0.900	0.080	0.000	0.070	4.073			1.18	*18*	1.18
1-octene	0.094	0.080	0.000	0.070	3.568			1.07	*18*	1.07
1,1,1-trifluoro-2,2-dichloroethane	−0.160	0.400	0.220	0.000	1.746			0.61	*12*	0.61
2,3,4-trimethylpentane	0.000	0.000	0.000	0.000	3.481			0.57	*6, 7*	0.57
2-methylheptane	0.000	0.000	0.000	0.000	3.480			0.49	*18*	0.49
2-methylnonane	0.000	0.000	0.000	0.000	4.453			0.76	*18*	0.76
2-methyloctane	0.000	0.000	0.000	0.000	3.966			0.52	*18*	0.52
allyl chloride	0.327	0.560	0.000	0.050	2.109			1.24	*6, 7*	1.24
bromobenzene	0.882	0.730	0.000	0.090	4.041			1.72	*22*	1.72
butane	0.000	0.000	0.000	0.000	1.615			−0.53	*7*	−0.53
cyanoethylene oxide	0.390	1.000	0.000	0.520	2.543			3.22	*25*	3.22
cycloheptane	0.350	0.100	0.000	0.000	3.704			0.72	*7*	0.72
cyclopentane	0.263	0.100	0.000	0.000	2.477			0.24	*7*	0.24
dibromomethane	0.714	0.690	0.110	0.070	2.886			1.87	*6, 7*	1.87
difluoromethane	−0.320	0.490	0.060	0.050	0.040			0.20	*6, 7*	0.20
fluorobenzene	0.477	0.570	0.000	0.100	2.788			1.06	*7*	1.06
fluorochloromethane	−0.080	0.270	0.090	0.030	1.030			0.71	*6, 7*	0.71
furan	0.369	0.510	0.000	0.130	1.913			0.82	*9*	0.82
hexafluorobenzene	0.088	0.560	0.000	0.010	2.345			0.39	*7*	0.39
2,3,4,5,6-pentafluorotoluene	0.240	0.450	0.040	0.000	0.946			0.73	*7*	0.73
3-methylstyrene	0.866	0.650	0.000	0.180	4.375			2.28	*6, 7*	2.28
pentachloroethane	0.648	0.660	0.170	0.060	4.267			2.02	*6, 7*	2.02
pentafluorobenzene	0.154	0.680	0.000	0.020	2.578			0.51	*7*	0.51
4-methylstyrene	0.871	0.650	0.000	0.180	4.399			2.37	*6, 7*	2.37
radon	0.000	0.000	0.000	0.000	0.877			−0.39	*15*	−0.39
tert-butylbenzene	0.619	0.490	0.000	0.180	4.413			1.24	*17*	1.24
tert-butylcyclohexane	0.300	0.100	0.000	0.100	4.603			1.16	*17*	1.16
tert-pentyl alcohol	0.194	0.300	0.310	0.600	2.630			2.59	*19*	2.59
1,1-difluoroethene	−0.100	0.000	0.000	0.050	0.240			−0.74	*14*	−0.74

Table 3. Comparison of Log K_{blood} (Human) and Log K_{blood} (Rat) for 86 Compounds

statistic	value
N	86
AE	0.124
AAE	0.210
SD	0.280
RMSE	0.279

Table 4. Interlaboratory Variation of Log K_{blood} (Human) for Three VOCs[a]

propanone	$CHCl_3$	trichloroethene
1.68 (26)	0.84 (6)	0.91 (6)
2.27 (5)	0.91 (36)	0.94 (4)
2.39 (34)	1.01 (37)	0.95 (36)
2.50 (4)	1.03 (32)	0.98 (37)
2.50 (35)	1.09 (4)	1.08 (38)
	0.93 (40)	0.96 (40)
SD = 0.34	SD = 0.09	SD = 0.06

[a] References in parentheses.

and $F = 242$. We can compare the errors on the coefficients in eqs 5 and 6 to see if they are statistically the same or not. Details of the SD values and the 95% confidence limits are in Table 5. The c coefficient is not the same in eqs 5 and 6, and the l coefficient is only just the same according to the 95% confidence limits. The other coefficients are statistically the same, and so, bearing in mind that the data sets are different, we conclude that the equations for log K_{blood} (human) and log K_{blood} (rat) are comparable.

Table 5. Comparison of Coefficients for Regression Equations for Log K_{blood} (Human) and Log K_{blood} (Rat)

	log K_{blood} (human)		log K_{blood} (rat)	
	95% limits	SD	95% limits	SD
c	−1.29 to −1.06	0.06	−0.93 to −0.58	0.09
e	0.17−0.62	0.11	0.29−0.84	0.14
s	0.71−1.24	0.13	0.78−1.33	0.14
a	3.24−4.36	0.28	3.08−4.19	0.28
b	2.38−3.00	0.16	2.07−2.76	0.17
l	0.36−0.46	0.03	0.23−0.35	0.03

Finally, we can average the data for log K_{blood} (human) and log K_{blood} (rat) to yield values for 196 compounds, by far the largest data set assembled. To assess the predictive capability of any equation, we divide the data into two sets, set (i) and set (ii). We use set (i) as a training set, to obtain an equation, and set (ii) as an independent test set that is used only for predictive assessment. In

Table 6. Coefficients in the LFER, eq 3, for Water and Solvents at 25 °C and for Blood at 37 °C

solvent	no.	c	e	s	a	b	l
water	1	−1.271	0.822	2.743	3.904	4.814	−0.213
human/rat blood	2	−1.069	0.456	1.083	3.738	2.580	0.376
methanol (dry)	3	−0.004	−0.215	1.173	3.701	1.432	0.769
ethanol (dry)	4	0.012	−0.206	0.789	3.635	1.311	0.853
octan-1-ol (wet)	5	−0.198	0.002	0.709	3.519	1.429	0.858
trichloromethane (wet)	6	0.116	−0.467	1.203	0.138	1.432	0.994
tetrachloromethane (wet)	7	0.282	−0.303	0.460	0.000	0.000	1.047
hexane (dry/wet)	8	0.292	−0.169	0.000	0.000	0.000	0.979
hexadecane (dry/wet)	9	0.000	0.000	0.000	0.000	0.000	1.000
toluene (dry/wet)	10	0.121	−0.222	0.938	0.467	0.099	1.012
diethyl ether (wet)	11	0.206	−0.169	0.873	3.402	0.000	0.882
ethylene glycol (dry)	12	−0.898	0.217	1.427	4.474	2.687	0.568
olive oil (dry/wet)	13	−0.230	0.009	0.795	1.353	0.000	0.888
acetonitrile (dry)	14	−0.007	−0.595	2.461	2.085	0.418	0.738

order that the chemical space for the two sets is the same, each set contained 98 compounds, and we selected the sets using the method of Kennard and Stone. (*46*). For the training set (i), we find that

$$\log K_{\mathrm{blood}}\,(\text{human or rat}),\ \text{set (i)} = -0.978 + 0.596\ \mathrm{E} + 1.000\ \mathrm{S} + 3.494\ \mathrm{A} + 2.914\ \mathrm{B} + 0.329\ \mathrm{L} \quad (7)$$

where $N = 98$, $R^2 = 0.933$, SD = 0.338, RMSE = 0.328, and $F = 257.3$. Equation 7 can then be used to predict values for the 98 compounds in the test set (ii). For the predicted and experimental values, we find that SD = 0.327, RMSE = 0.326, AAE = 0.255, and AE = 0.043 log units. There is therefore no bias in the predictions using eq 7, with AE equal to only 0.043 log units.

To confirm that our predictive assessment is firmly based, we then used set (ii) as the training set and obtained the equation

$$\log K_{\mathrm{blood}}\,(\text{human or rat}),\ \text{set (ii)} = -1.153 + 0.095\ \mathrm{E} + 1.446\ \mathrm{S} + 4.275\ \mathrm{A} + 1.921\ \mathrm{B} + 0.422\ \mathrm{L} \quad (8)$$

where $N = 98$, $R^2 = 0.950$, SD = 0.295, RMSE = 0.286, and $F = 348.9$. Then, eq 8 can be used to predict values in the test set (i), for which we find SD = 0.393, RMSE = 0.391, AAE = 0.293, and AE = 0.006 log units. Taking both test sets together, there is no bias at all in the predictions, with AE = 0.043 and 0.006 log units. The equations are capable of predicting further values of log K_{blood} (human or rat), to around 0.30 log units, as judged from the SD and AAE values for the two test sets. This appears to be the first time that any predictive assessment of calculations for log K_{blood} has been made through the method of training and test sets.

Finally, we can combine the test and training sets and obtain a general equation for the 196 compounds (eq 9). We suggest that eq 9 be used if predictions of log K_{blood} (human or rat) are required.

$$\log K_{\mathrm{blood}}\,(\text{human or rat}) = -1.069 + 0.456\ \mathrm{E} + 1.083\ \mathrm{S} + 3.738\ \mathrm{A} + 2.580\ \mathrm{B} + 0.376\ \mathrm{L} \quad (9)$$

where $N = 196$, $R^2 = 0.938$, SD = 0.324, RMSE = 0.319, and $F = 572.8$. The p values for the constant and the coefficients in eq 9 are 8×10^{-6} for the e coefficient and less than 8×10^{-18} for the rest. We can use the data on human blood and rat blood without averaging the K_{blood} (human) and K_{blood} (rat) values. This leads to 282 data points but for 196 compounds. The corresponding equation is

$$\log K_{\mathrm{blood}}\,(\text{human or rat}) = -1.062 + 0.460\ \mathrm{E} + 1.067\ \mathrm{S} + 3.777\ \mathrm{A} + 2.556\ \mathrm{B} + 0.375\ \mathrm{L} \quad (10)$$

where $N = 282$ (196), $R^2 = 0.927$, SD = 0.330, RMSE = 0.323, and $F = 699.1$. The coefficients in eqs 9 and 10 are almost identical. The R^2 value in eq 10 is a little less than that in eq 9, but the F statistic is much better, simply reflecting the larger number of data points.

In all of our equations based on the general equation, eq 3, we include all five variables, so that no stepwise regression is needed. The e. E term is often not significant, as shown by the p values (t-test) for eq 9 as an example. However, we prefer to retain all five terms, rather than to reduce the equation to one with four terms. There is little advantage in a four term equation as regards calculation, and there is a decided advantage in keeping all five terms when coefficients in equations are compared, as we shall do later.

The statistics for our correlation equations, eqs 7−10, are not quite as good as those for other equations summarized in Table 1 in terms of R^2 and SD. We can only compare the predictive power of our equations with results from Poulin and Krishnan (*42*). We conclude that whereas our equations are expected to predict log K_{blood} (human or rat) to 0.33 log units, the method of Poulin and Krishnan has a predictive capability of 0.58 log units—probably too high to be of much practical use. Previous correlation equations have used partition coefficients for air to oil and air to saline as descriptors. This restricts the number of log K_{blood} values that can be predicted from data already available, because of lack of the required partition coefficients. In addition, no predictions can be made from structure unless log K_{oil} and log K_{saline} can be predicted from structure. The descriptors required for our method are available for some 3000 compounds (*45*), for which log K_{blood} could be predicted immediately. In addition, the descriptors can be calculated from structure (*45*), so that log K_{blood} can be predicted for any given chemical structure.

Because the descriptors in the LFER, eq 3, refer to specific chemical interactions, the coefficients in any LFER obtained through eq 3 must be chemically realistic and must reflect the chemical properties of the solvent or condensed phase. In Table 6 are collected coefficients in eq 3 for various air to solvent partitions, together with the coefficients in eq 9. Those for the solvents are at 25 °C, rather than 37 °C, but preliminary results suggest that this makes little difference (*1*). The solvents that

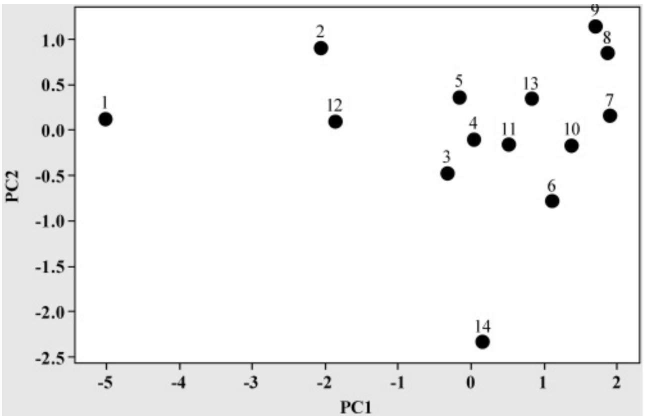

Figure 1. Principal component score plot for the air to condensed phase processes shown in Table 6. Points are numbered as in Table 6.

blood most resembles are water and the alcohols, including ethylene glycol. Like these solvents, blood is dipolar/polarizable ($s = 1.083$) and is a strong hydrogen bond base ($a = 3.738$) and a strong hydrogen bond acid ($b = 2.580$). As regards the e coefficient, blood is between the water and the alcohols. More important is the l coefficient, which we take as a measure of solvent hydrophobicity. Of the solvents listed in Table 6, alkanes, tetrachloromethane, and toluene are the most hydrophobic, as expected. Of pure solvents, water is the only one with a negative value of the l coefficient. Blood is again between the water and the alcohols and ethylene glycol, as regards hydrophobicity, not surprising considering that blood contains a collection of hydrophobic materials such as protein. It appears, therefore, that the coefficients in eq 9 are not just fitting coefficients but encode information on the chemical properties of blood that influence solubility in blood.

It is not very easy to compare solvents just by inspection of coefficients, but a useful visual comparison is through principal component analysis (PCA). The five columns of coefficients in Table 6 (excluding the c constant) can be manipulated through PCA into five columns of orthogonal principal components. The first two columns of principal components contain 87% of the total information of the five columns of coefficients. A score plot of PC2 against PC1, as given in Figure 1, then shows visually how near the coefficients are to each other and hence how near the solvents or phases are to each other in chemical terms. Ethylene glycol (no. 12) is the nearest to blood (no. 2), because it has large positive s, a, and b coefficients and a comparatively small l coefficient. Interestingly, octan-1-ol (no. 5), which is often suggested as a model for biological phases, is a poor model for blood. We can predict that any condensed phase that has large positive s, a, and b coefficients and a small negative l coefficient will be a reasonable chemical model for blood in terms of solute-condensed phase interactions. The PCA was carried out using minitab software (*47*), which was also used for the various statistical analyses and multiple linear regression.

In conclusion, we show that for a large data set of air to blood partitions for VOCs it is possible to construct a statistically sound model and to assess the predictive capability of the model through selection of training and test sets of VOCs. A particular feature of the model is that the coefficients obtained are not just fitting parameters but encode chemical information about the nature of the process. This enables the air to blood process to be compared to various other air to solvent phase processes and to examine the factors that influence interactions between VOCs and blood.

Acknowledgment. We thank Dr. Chris Luscombe for help with the Stone−Kennard method.

References

(1) Abraham, M. H., and Weathersby, P. K. (1994) Hydrogen bonding. 30. Solubility of gases and vapours in biological liquids and tissues. *J. Pharm. Sci. 83*, 1450−1455.
(2) Filser, J. G., Csanady, Gy. A., Hartmann, M., Denk, B., Kauffmann, A., Kessler, W., Kreuzer, P. E., Putz, C., Shen, J. H., and Stei, P. (1996) Toxicokinetics of isoprene in rodents and humans. *Toxicology 113*, 278−287.
(3) Filser, J. G., Schmidbauer, R., Rampf, F., Baur, C. M., Putz, C., and Csanady, G. A. (2000) Toxicokinetics of inhaled propylene in mouse, rat, and human. *Toxicol. Appl. Pharmacol*. *169*, 40−51.
(4) Imbriani, M., Ghittori, S., Pezzagno, G., and Capodagio, E. (1985) Urine/air partition coefficients for some industrially important substances. *G. Ital. Med. Lav. 7*, 133−140.
(5) Fiserova-Bergerova, V., and Diaz, M. L. (1986) Determination and prediction of tissue-gas partition coefficients. *Int. Arch. Occup. Environ. Health 58*, 75−87.
(6) Gargas, M. L., Burgess, R. J., Voisard, D. E., Cason, G. H., and Anderson, M. E. (1989) Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. *Toxicol. Appl. Pharmacol. 98*, 87−99.
(7) Meulenberg, C. J. W., and Vijverberg, H. P. M. (2000) Empirical relations predicting human and rat tissues: Air partition coefficients of volatile organic compounds. *Toxicol. Appl. Pharmacol. 165*, 206−216.
(8) Kaneko, T., Kim, H. Y., Wang, P. Y., and Sato, A. (1997) Partition coefficients and hepatic metabolism in vitro of 1- and 2-bromopropanes. *J. Occup. Health 39*, 341−342.
(9) Kedderis, G. L., Carfagna, M. A., Held, S. D., Batra, R., Murphy, J. E., and Gargas, M. L. (1993) Kinetic analysis of furan biotransformation by F-344 rats in vivo and in vitro. *Toxicol. Appl. Pharmacol. 123*, 274−282.
(10) Knaak, J. B., and Smith, L. W. (1998) In vitro hepatic metabolism of PCBTF: Development of Vmax and Km values and partition coefficients and their use in an inhalation PBPK model. *Inhalation Toxicol. 10*, 65−85.
(11) Borghoff, S. J., Murphy, J. E., and Medinsky, M. A. (1996) Development of a physiological based pharmacokinetic model for methyl tertiary-butyl ether and tertiary-butanol in male Fischer-344 rats. *Fundam. Appl. Toxicol. 30*, 264−275.
(12) Loizou, G. D., Urban, G., Dekant, W., and Anders, M. W. (1994) Gas uptake pharmacokinetics of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). *Drug Metab. Dispos. 22*, 511−517.
(13) Loizou, G. D., and Anders, M. W. (1993) Gas uptake pharmacokinetics and biotransformation of 1,1-dichloro-1-fluoroethane (HCFC-141b). *Drug Metab. Dispos. 21*, 634−639.
(14) Medinsky, M. A., Bechtold, W. E., Birnbaum, L. S., Chico, D. M., Gerlach, R. F., and Henderson, R. F. (1988) Uptake of vinylidene fluoride in rats simulated by a physiological model. *Fundam. Appl. Toxicol. 11*, 250−260.
(15) Nussbaum, E., and Hursh, J. B. (1957) Radon solubility in rat tissues. *Science 125*, 552−553.
(16) Zahlsen, K., and Eide, I. (1996) Inhalation experiments with mixtures of hydrocarbons. *Arch. Toxicol. 70*, 397−404.
(17) Zahlsen, K., Eide, I., Nilsen, A. M., and Nisen, O. G. (1992) Inhalation kinetics of C6 to C10 aliphatic, aromatic and naphthetic hydrocarbons in rat after repeated exposures. *Pharmacol. Toxicol. 71*, 144−149.
(18) Zahlsen, K., Eide, I., Nilsen, A. M., and Nisen, O. G. (1993) Inhalation kinetics of C8 to C10 1-alkenes and isoalkanes in the rat after repeated exposures. *Pharmacol. Toxicol. 73*, 163−168.
(19) Kaneko, T., Wang, P.-Y., and Sato, A. (2000) Partition coefficients for gasoline additives and their metabolites. *J. Occup. Health 42*, 86−87.
(20) Johanson, G., and Dynesius, B. (1988) Liquid/air partition of six commonly used glycol ethers. *Br. J. Ind. Med. 45*, 561−564.
(21) Sweeney, L. M., Himmelstein, M. W., and Gargas, M. L. (2001) Development of a preliminary physiological based toxicokinetic (PBTK) model for 1,3-butadiene risk assessment. *Chem.-Biol. Interact. 135−136*, 303−322.

(22) Morris, J. B., Hassett, D. N., and Blanchard, K. T. (1993) A physiologically based pharmacokinetics model for nasal uptake and metabolism of nonreactive vapors. *Toxicol. Appl. Pharmacol*. *123*, 120−129.

(23) Krishnan, K., Gargas, M. L., Fennell, T. R., and Anderson, M. E. (1992) A physiologically based description of ethylene oxide dosimetry in the rat. *Toxicol. Ind. Health 8*, 121−140.

(24) Csanady, Gy. A., Kreuzer, P. E., Baur, C., and Filser, J. G. (1996) A physiologically toxicokinetic model for 1,3-butadiene in rodents and man: Blood concentrations of 1,3-butadiene, its metabolically formed epoxides, and of haemoglobin adducts- relevance of glutathione depletion. *Toxicology 113*, 300−305.

(25) Gargas, M. L., Anderson, M. E., Teo, S. K. O., Batra, R., Fennell, T. R., and Kedderis, G. L. (1995) A physiologically based dosimetry description of acrylonitrile and cyanoethylene in the rat. *Toxicol. Appl. Pharmacol. 134*, 185−194.

(26) Guitart, R. (1993) Solubilidad de seis gases en sangre y en diversos medios liquidos. *Rev. Esp. Fisiol. 49*, 195−202.

(27) Barton, H. A., Creech, J. R., Godin, C. S., Randall, G. M., and Seckel, C. S. (1995) Chloroethylene mixtures: Pharmacokinetics modeling and in vitro metabolism of vinyl chloride, trichloroethylene, and *trans*-1,2-dichloroethylene in rat. *Toxicol. Appl. Pharmacol*. *130*, 237−247.

(28) Simmons, J. E., Boyes, W. K., Bushnell, P. J., Raymer, J. H., Limsakun, T., McDonald, A., Sey, Y. M., and Evans, M. V. (2002) A physiologically based pharmacokinetic model for trichloroethylene in the male Long-Evans rat. *Toxicol. Sci. 69*, 3−15.

(29) Csanady, Gy. A., Denk, B., Putz, C., Kreuzer, Kessler, W., Baur, C., Gargas, M. L., and Filser, J. G. (2000) A physiological toxicokinetic model for exogenous and endogenous ethylene and ethylene oxide in rat, mouse, and human: Formation of 2-hydroxyethyl adducts with hemoglobin and DNA. *Toxicol. Appl. Pharmacol. 165*, 1−26.

(30) Reitz, R. H., Gargas, M. L., Anderson, M. E., Provan, W. M., and Green, T. L. (1996) Predicting cancer risk from vinyl chloride exposure with a physiological based pharmacokinetic model. *Toxicol. Appl. Pharmacol. 137*, 253−267.

(31) Beliveau, M., Charest-Tardif, G., and Krishnan, K. (2001) Blood: air partition coefficients of individual and mixtures of trihalomethanes. *Chemosphere 44*, 377−381.

(32) Batterman, S., Zhang, L., Wang, S., and Franzblau, A. (2002) Partition coefficients for the trihalomethanes among blood, urine, water, milk and air. *Sci. Total Environ. 284*, 237−247.

(33) Lilly, P. D., Anderson, M. E., Ross, T. M., and Pegram, R. A. (1997) Physiological based estimation of in vivo rates of bromodichloromethanes metabolism. *Toxicology 124*, 141−152.

(34) Sato, A., and Nakajima, T. (1979) Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. *Br. J. Ind. Med. 36*, 231−234.

(35) Young, I. H., and Wagner, P. D. (1979) Effect of intrapulmonary hematocrit maldistribution on O_2, CO_2 and inert gas exchange. *J. Appl. Physiol. 46*, 240−248.

(36) Sherwood, R. J. (1976) Ostwald solubility coefficients of some industrially important substances. *Br. J. Ind. Med. 33*, 106−107.

(37) Sato, A., and Nakajima, T. (1979) A structure−activity relationship of some chlorinated hydrocarbons. *Arch. Environ. Health. 34*, 69−75.

(38) Wilson, P. F., Freeman, C. G., McEwan, M. J., Allardyce, R. A., and Shaw, G. M. (2003) SIFT-MS measurement of VOC distribution coefficient in human blood constituents and urine. *Appl. Occup. Environ. Hyg. 18*, 759−763.

(39) Kaneke, T., Wang, P.-Y., and Sata, A. (1994) Partition coefficients of some acetate esters and alcohols in water, blood, olive oil and rat tissues. *Occup. Environ. Med. 51*, 68−72.

(40) Thrall, K. D., Gies, R. A., Muniz, J., Woodstock, A. D., and Higgins, G. (2002) Route-of-entry and brain tissue partition coefficients for common superfund contaminants. *J. Toxicol. Environ. Health A 65*, 2075−2086.

(41) Beliveau, M., and Krishnan, K. (2000) Estimation of rat blood: air partition coefficients of volatile organic chemicals using reconstituted mixtures of blood components. *Toxicol. Lett. 116*, 183−188.

(42) Poulin, P., and Krishnan, K. (1996) A mechanistic algorithm for predicting blood-air partition coefficients of organic chemicals with the consideration of reversible binding in hemoglobin. *Toxicol. Appl. Pharmacol. 136*, 131−137.

(43) Abraham, M. H. (1993) Scales of hydrogen bonding: Their construction and application to physicochemical and biochemical processes. *Chem. Soc. Rev. 22*, 73−83.

(44) Abraham, M. H., Ibrahim, A., and Zissimos, A. M. (2004) The determination of sets of solute descriptors from chromatographic measurements. *J. Chromatogr. A 1037*, 29−47.

(45) *PharmaAlgorithms, ADME Boxes*, Version 2.2, PharmaAlgorithms Inc., Toronto, ON, Canada.

(46) Kennard, R. W., and Stone, L. A. (1959) Computer aided design of experiments. *Technometrics 11*, 137−148.

(47) *Minitab*, Version 14 (2003) Minitab Inc., State College, PA.

TX050066D