Air to Muscle and Blood/Plasma to Muscle Distribution of Volatile Organic Compounds and Drugs: Linear Free Energy Analyses

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Received December 2, 2005

Distribution coefficients, K_{mus} , from the gas phase to the muscle have been collected for volatile organic compounds (VOCs). For 114 VOCs, a linear free energy relationship (LFER) yields an equation for $\log K_{mus}$ with $R^2 = 0.944$ and $SD = 0.267$; construction of a training and test set shows that the LFER can predict further values to around 0.30 log units. The combination of the $\log K_{mus}$ values with values for air to blood yields distribution coefficients from blood to muscle, $\log P_{mus}$, for 110 VOCs; the corresponding LFER has $R^2 = 0.537$ and $SD = 0.207$ and a predictive capability of 0.22 log units. We also collected data on the distribution of drugs from blood or plasma to muscle and showed that the two sets of data can be combined. A LFER for blood/plasma to muscle for 59 drugs has $R^2 = 0.745$ and $SD = 0.253$ and a predictive capability of 0.25 log units. Finally, we show that the in vitro data on VOCs and the in vivo data on drugs can be combined; a LFER on the total data for 163 compounds has $R^2 = 0.595$, $SD = 0.220$, and a predictive capability of about 0.25 log units.

Introduction

The distribution of volatile organic compounds (VOCs) from air to muscle is of importance in environmental and toxicological sciences, and there have been a considerable number of citations of air to muscle distribution data for VOCs (1–17). We have collected available data and give in Table 1 a list of air to muscle distribution data for VOCs, as $\log K_{mus}$, where the defining equation for air to muscle partition, at 37 °C, is

$$K_{mus} = \frac{[\text{concentration of compound in muscle}]}{[\text{concentration of compound in air}]} \quad (1)$$

The values of $\log K_{mus}$ for the VOCs are in vitro data, obtained by measurement of gas/vapor solubilities in isolated human or rat muscle. We use the term $\log K_{mus}$ for the compounds in Table 1, even though they include a few volatile inorganic compounds. Although there has been much activity with regard to measurement and collection of data, there have been but few attempts to set up equations for the correlation and prediction of $\log K_{mus}$ values.

Meulenberg and Vijverberg (1) obtained correlative equations for air to muscle distribution in rats and humans. They found that the partition coefficients of VOCs in human (or rat) could be described by a linear combination of air to oil, K_{oil} , and air to saline, K_{saline} , partition coefficients, as shown in eqs 2 and 3, where values for human muscle and rat muscle were analyzed separately.

$$K_{mus}(\text{human}) = 0.014K_{oil} + 0.384K_{saline} + 0.94 \quad (2)$$

where $N = 35$, $R^2 = 0.99$, and $SD = n/a$.

$$K_{mus}(\text{rat}) = 0.010K_{oil} + 0.772K_{saline} + 0.29 \quad (3)$$

where $N = 76$, $R^2 = 0.82$, and $SD = n/a$.

In eqs 2 and 3 and in other statistics, N is the number of data points, R is the correlation coefficient, SD is the regression standard deviation, $RMSE$ is the root-mean-square deviation, and F is the F statistic. Gargas et al. (3) also modeled the air to muscle partition coefficient on the same lines as Meulenberg and Vijverberg (1), but this time, they used $\log K_{mus}$ as in eq 4.

$$\log K_{mus} = 0.644(\pm 0.038) \log K_{oil} + 0.180(\pm 0.032) \log K_{saline} - 0.725(\pm 0.104) \quad (4)$$

where $N = 55$, $R^2 = 0.879$, and $RMSE = 0.233$. Abraham and Weathersby (4) correlated 41 values of $\log K_{mus}$ (human) with the descriptors **E**, **S**, **A**, **B**, and **L** as shown in eq 5. We describe these Abraham descriptors in detail later.

$$\log K_{mus}(\text{human}) = -1.140 + 0.544\mathbf{E} + 0.216\mathbf{S} + 3.471\mathbf{A} + 2.924\mathbf{B} + 0.578\mathbf{L} \quad (5)$$

where $N = 41$, $R^2 = 0.966$, and $SD = 0.262$. Although eqs 2–5 are statistically very good fits of the data, none of them has been assessed with respect to predictive power.

Values of $\log K_{mus}$ can then be combined with corresponding values of the gas to blood partition coefficient, as $\log K_{blood}$, to obtain the in vitro blood to muscle partition coefficient, as $\log P_{mus}$, for VOCs. Fiserova-Bergerova and Diaz (2) obtained a rather poor equation in terms of the corresponding blood to fat partition, eq 6

$$P_{mus} = 0.0326P_{fat} + 0.4504 \quad (6)$$

where $N = 34$, $R^2 = 0.928$, and $SD = 0.702$. Abraham and Weathersby (4) used the Abraham descriptors to fit a similar data set according to eq 7. These descriptors are fully discussed

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Table 1. Values of log K_{mus} (Human) and log K_{mus} (Rat) for VOCs

solute ^a	human		rat		avg log K_{mus}	calcd ^b log K_{mus}
	log K_{mus}	ref	log K_{mus}	ref		
(CF ₃) ₂ CHOCH ₂ F (sevoflurane)*	0.22	1, 2, 4			0.22	0.44
1,1,1,2-tetrachloroethane*			1.60	1, 3	1.60	1.74
1,1,1-trichloroethane	0.83	1, 2, 4	0.50	1, 3	0.67	0.82
1,1,2,2-tetrachloroethane*			2.00	1, 3	2.00	2.21
1,1,2-trichloroethane			1.36	1, 3	1.36	1.82
1,1-dichloroethane*			0.71	1, 3	0.71	1.03
1,1-dichloroethylene			0.31	1, 3	0.31	0.38
1,1-dichloro-1-fluoroethane*			0.02	11	0.02	0.33
1,2-dibromoethane			1.66	1, 3	1.66	1.97
1,2-dichloroethane*			1.37	1, 3	1.37	1.30
1,2-dichloropropane*			1.08	1, 3	1.08	1.23
1,3-butadiene	-0.06	5			-0.06	0.16
1,2-epoxy-3-butene*			1.66	16	1.66	1.31
1-bromo-2-chloroethane			1.40	1, 3	1.40	1.51
1-butanol			2.95	1	2.95	2.90
1-chloropropane			0.32	1, 3	0.32	0.56
1-nitropropane*			1.46	1, 3	1.46	1.80
1-pentanol*			2.91	1	2.91	3.13
1-propanol	2.83	1, 2, 4	3.06	1	2.95	2.64
2,2,4-trimethylpentane			0.52	1, 3	0.52	0.40
2,2-dimethylbutane	0.00	1, 2, 4			0.00	0.05
2,2-dichloro-1,1,1-trifluoroethane*			0.39	12	0.39	0.74
2,3,4-trimethylpentane			0.64	1, 3	0.64	0.57
2-chloropropane			0.31	1, 3	0.31	0.46
2-heptanone			2.33	1	2.33	2.48
2-methyl-1,3-butadiene			0.26	1, 3, 13	0.26	0.41
2-methyl-1-propanol	2.54	1, 2, 4	2.93	1	2.74	2.79
2-methylpentane	0.46	1, 2, 4			0.46	0.12
2-nitropropane			1.46	1, 3	1.46	1.67
2-pentanone			2.00	1	2.00	2.02
2-propanol*	2.70	1, 2, 4	3.04	1	2.87	2.53
3-methyl-1-butanol			2.90	1	2.90	3.06
3-methylhexane	1.04	1, 2, 4			1.04	0.37
3-methylpentane	0.58	1, 2, 4			0.58	0.16
4-methyl-2-pentanone			1.81	1	1.81	2.14
propanone	2.18	1, 2, 4	2.23	1	2.21	1.63
acetylene*	0.03	4			0.03	-0.21
allyl chloride*			1.04	1, 3	1.04	0.53
argon	-1.64	4			-1.64	-1.36
benzene*	1.21	1, 2, 4	1.01	1, 3	1.11	1.10
bromochloromethane*			1.05	1, 3	1.05	0.96
butan-2-one*	2.01	1, 2, 4	2.26	1	2.14	1.82
butyl acetate			2.20	1	2.20	2.07
tetrachloromethane*			0.66	1, 3	0.66	0.64
1-chloro-2,2-difluoroethylene*	0.00	2, 4			0.00	-0.08
CF ₃ CBrClH (halothane)*	0.83	1, 2, 4	0.65	1, 3	0.74	0.87
CF ₃ CBrFH (teflurane)*	0.34	2, 4			0.34	0.43
1-chloro-2,2,2-trifluoroethane*	0.34	1, 2, 4	0.09	1, 3	0.22	0.28
CF ₃ CH ₂ OCH=CH ₂ (fluroxene)*	0.35	1, 2, 4			0.35	0.62
CHF ₂ OCF ₂ CHFCI (enflurane)	0.64	1, 2, 4			0.64	0.72
CHF ₂ OCHClCF ₃ (isoflurane)*	0.41	1, 2, 4	0.20	1, 3	0.31	0.57
chlorobenzene*			1.53	1, 3	1.53	1.45
chlorodibromomethane*			1.75	1, 3	1.75	1.59
chloroethane			0.51	1, 3	0.51	0.32
chloroform*	1.09	1, 2, 4	1.14	1, 3	1.12	1.09
cis-1,2-dichloroethylene			0.78	1, 3	0.78	1.06
cyclohexane*	1.02	1, 2, 4	0.01	1, 3	0.52	0.47
cyclopropane*	-0.31	1, 2, 4			-0.31	-0.18
dibromomethane			1.61	1, 3	1.61	1.47
dichloromethane	0.68	1, 2, 4	0.90	1, 3	0.79	0.84
diethyl ether*	1.01	1, 2, 4	0.72	1, 3	0.87	1.19
difluoromethane*			0.16	1, 3	0.16	-0.41
divinyl ether	0.34	1, 2, 4			0.34	0.43
ethanol*	2.93	1, 2, 4	3.23	1	3.08	2.39
ethyl acetate			1.84	1	1.84	1.61
ethyl tert-butyl ether*			1.35	6	1.35	1.81
2-methyl-2-propanol			2.80	6, 17	2.80	2.61
methyl tert-butyl ether			1.57	6	1.57	1.68
methyl tert-amyl ether			1.38	6	1.38	1.95
tert-amyl alcohol*			2.59	6	2.59	2.92
ethylbenzene*			1.41	1	1.41	1.58
ethylene oxide*	1.82	15	1.68	14	1.75	1.20
ethylene	-0.19	15	-0.20	15	-0.20	-0.64
fluorochloromethane*			0.39	1, 3	0.39	-0.02
helium*	-1.93	4			-1.93	-1.84

Table 1. (Continued)

solute ^a	human		rat		avg log <i>K</i> _{mus}	calcd ^b log <i>K</i> _{mus}
	log <i>K</i> _{mus}	ref	log <i>K</i> _{mus}	ref		
heptane	1.08	1, 2, 4	0.62	1, 3	0.85	0.43
hexachloroethane*			1.88	1, 3	1.88	1.78
hexane	0.70	1, 2, 4	0.46	1, 3	0.58	0.20
hydrogen	-1.76	4			-1.76	-1.59
isobutyl acetate			2.04	1	2.04	2.01
isopentyl acetate*			2.32	1	2.32	2.28
isopropyl acetate			1.85	1	1.85	1.72
isopropyl bromide*			0.61	1, 3	0.61	0.74
krypton	-1.38	4			-1.38	-1.14
MeOCF ₂ CHCl ₂ (methoxyflurane)*	1.35	1, 2, 4			1.35	1.37
methane*	-1.41	4			-1.41	-1.19
methyl acetate			1.81	1	1.81	1.45
methyl chloride*			-0.01	1, 3	-0.01	0.06
methylcyclopentane	0.70	1, 2, 4			0.70	0.43
m-methylstyrene			2.26	1, 3	2.26	2.08
m-xylene			1.62	1, 3	1.62	1.64
nitrous oxide*	-0.43	2, 4			-0.43	-0.45
octane*	0.93	1, 4			0.93	0.66
o-xylene			1.71	1, 3	1.71	1.72
pentachloroethane*			1.86	1, 3	1.86	2.25
pentane*	-0.15	1, 2, 4			-0.15	-0.04
pentyl acetate			2.36	1	2.36	2.30
p-methylstyrene*			2.26	1, 3	2.26	2.09
propyl acetate*			1.93	1	1.93	1.83
1-bromopropane			0.62	1, 3	0.62	0.84
propylene*	-0.19	7	-0.34	7	-0.27	-0.35
p-xylene			1.58	1, 3	1.58	1.64
radon			-0.81	8	-0.81	-0.63
styrene			1.67	1, 3	1.67	1.79
sulfur hexafluoride*	-1.85	4			-1.85	-1.36
tetrachloroethylene*			1.30	1, 3	1.30	1.07
toluene	1.54	1, 2, 4	1.44	1, 3	1.49	1.35
trans-1,2-dichloroethylene			0.55	1, 3	0.55	0.82
trichloroethylene*	1.25	1, 2, 4	1.00	1, 3	1.13	1.06
vinyl bromide*			0.35	1, 3	0.35	0.47
vinyl chloride			0.32	1, 3	0.32	0.06
1,1-difluoroethylene*			-0.54	10	-0.54	-0.67
xenon	-1.00	2			-1.00	-0.86
difluorochloromethane*	0.03	4			0.03	0.11
JP-10 ^c			2.83	3	2.83	1.86
methanol ^f	3.12	1, 2, 4	3.60	1	3.36	2.46
4-chlorobenzotrifluoride ^c			2.03	9	2.03	1.25

^a Values marked with * are the training set; the rest are the test set. ^b Calculated values for log *K* from eq 14. ^c Not used in the correlation; JP-10 is tricycle[5.2.1.0^{2,6}]decane.

in the Methods and Results section below.

$$\text{Log } P_{\text{mus}} = -0.222 - 0.479S - 0.517B + 0.999V \quad (7)$$

where $N = 40$, $R^2 = 0.790$, and $SD = 0.176$. More complicated expressions were used by Balaz and Lukacova (18) and by Zhang (19). 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. Because no fewer than seven adjustable variables were used to correlate values for 36 simple compounds, of which two were rejected as outliers, it is not surprising that the statistics for the fitting equation are excellent. No assessment of predictive ability was made.

$$\text{Log } P_{\text{mus}} = \log [(A_0 + A_1 \times I_1 + A_2 \times I_2) P_{\text{oct}}^\beta] / [A_b \times P_{\text{oct}}^\beta + 1] + B \quad (8)$$

where $N = 34$, $R^2 = 0.908$, and $SD = 0.108$. Zhang (19) set out two initial equations, eqs 9 and 10, and then combined them to give eq 11, again for VOCs. The descriptors used are as follows: α is the molecular polarizability, $\sum Ca$ is the sum of H-bond factor values for all hydrogen bond acceptor substructures in the molecule, and $\sum Q^+$ is the sum of all positive partial

atomic charges for all atoms in the molecule. Once again, although the fit to eq 11 is very good, no predictive assessment was made.

$$\text{Log } P_{\text{lipid}} = 0.091\alpha - 0.760\sum Ca + 0.600\sum Q^+ \quad (9)$$

$$\text{Log } P_{\text{protein}} = 0.553\sum Q^+ \quad (10)$$

$$\text{Log } P_{\text{mus}} = \log(10^{\text{Log } P_{\text{lipid}}} + 10^{\text{Log } P_{\text{protein}}} + 1) - 0.617 \quad (11)$$

where $N = 36$, $R^2 = 0.884$, and $SD = 0.133$.

One aim of the present work is to collect more data on values of log K_{mus} and log P_{mus} for VOCs and then to construct equations that can be assessed for predictive capability power, not just for fitting power.

In principle, the same equations used to fit the in vitro values of log K_{mus} and of log P_{mus} for VOCs could be used to fit in vivo values of blood to muscle distribution for drugs. However, to our knowledge, no equations specifically for blood to muscle distribution of drugs have been published. Rodgers et al. (20, 21) have developed equations for the distribution of 20 drugs (some of which were as enantiomeric pairs) between plasma water and muscle. Poulin and Theil (22) developed a general equation for plasma to tissue distribution of drugs and included

plasma to muscle but gave no statistics for their prediction of plasma to muscle distribution. In any case, although the method of Poulin and Theil (22) is very general, it ultimately requires a knowledge of the drug water to vegetable oil partition and, hence, cannot be used to predict distribution from structure. We note, however, that in a subsequent paper (23), the water to vegetable oil partition has been replaced by the water to octanol partition for distribution into all tissues other than adipose.

The second aim of the present work is to collect data on *in vivo* values of blood or plasma to muscle distribution for drugs and again to construct equations that could be used for the prediction of further values. Whether or not the *in vitro* values for VOCs and the *in vivo* values for drugs can be combined will have to be ascertained. With regard to the equivalent data for air to blood, air to brain, and blood to brain distributions, we have already shown that the *in vitro* values for VOCs (24, 25) and the *in vivo* values for drugs (26) can only be combined in a general equation for blood to brain distribution if a systematic difference between the two sets of data is taken into account (26).

Methods and Results

Air to Muscle Distribution for VOCs. The data that we use on air to muscle distributions are in Table 1. There are 23 compounds for which $\log K_{\text{mus}}$ values are available for partition into both human and rat muscle. For one compound, cyclohexane, the values are so far apart as to suggest some possible error (1.02 and 0.01 log units). For the remaining 22 compounds, an analysis of the data yields an average error, $AE = -0.014$ (human–rat data), an absolute average error, $AAE = 0.256$, and a standard deviation, $SD = 0.299$ log units. The results are quite clear. The AE , which represents a systematic difference, is so small that the two sets can be combined or averaged. The AAE and SD values, which indicate the total (systematic and random) errors, then show that the experimental error in the measurements must be around 0.2–0.3 log units. We previously analyzed experimental data on air to human blood and air to rat blood, and for 86 compounds, we found that $AE = 0.124$ and $SD = 0.280$ log units (24). This is in good agreement with an analysis of Gargas et al. (3) who found that in a plot of $\log K_{\text{blood}}$ (human) against $\log K_{\text{blood}}$ (rat) there was an intercept of 0.232 log units. Because the systematic difference that we found, $AE = 0.124$, is considerably less than the total error, SD , we suggested (24) that values of $\log K_{\text{blood}}$ (human) and $\log K_{\text{blood}}$ (rat) for VOCs could be averaged. We can then combine the averaged data for $\log K_{\text{blood}}$ (human and rat) with the present data on $\log K_{\text{muscle}}$ (human and rat) to obtain *in vitro* blood to muscle partition coefficients, P_{mus} , for VOCs. Details are in Table 2, where the required air to blood partition coefficients, as $\log K_{\text{blood}}$, are taken from our previous compilation (24).

We have set out to use the Abraham solvation equations in the correlation and prediction of gas to blood and blood to brain partitions in some detail already (24–26). In brief, eqs 12 and 13 are used in multiple linear regression analyses of the dependent variables. Equation 12 is used for gas to condensed phase processes; in the present work, SP is $\log K_{\text{mus}}$. Equation 13 is used for processes within condensed phases, and in the present work, SP is $\log P_{\text{mus}}$.

$$SP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + l \cdot L \quad (12)$$

$$SP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \quad (13)$$

The independent variables in eqs 12 and 13 are VOC (or solute) properties, as discussed several times (24–28). E is the solute

excess molar refractivity in units of $(\text{dm}^3 \text{mol}^{-1})/10$, 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 $(\text{dm}^3 \text{mol}^{-1})/100$. E is obtained from the refractive index of the pure liquid compound at 20 °C; if the compound is a gas or solid, the refractive index can be estimated or E itself can be calculated quite easily (29). The descriptors S , A , B , and L are obtained from gas–liquid chromatographic measurements and water to solvent partition measurements, as described in detail (28); they can also be calculated just from structure (29). The important V descriptor is trivially calculated from the number and type of atoms and the number of rings in a molecule (27).

We used eqs 12 and 13 because they were known to yield excellent statistics for the corresponding equations for distribution into blood and brain (24–26) and, very importantly, because the necessary descriptors are available for several thousand VOCs and can be calculated from structure if required (29). All statistical analyses were carried out using Minitab, Version 14 (30).

Application of eq 12 to the $\log K_{\text{mus}}$ values in Table 1 yielded eq 14 for 114 VOCs, by far the largest set of compounds analyzed in this way; compare eqs 2–5.

$$\log K_{\text{mus}} = -1.039 + 0.207E + 0.723S + 3.242A + 2.469B + 0.463L \quad (14)$$

where $N = 114$, $R^2 = 0.944$, $SD = 0.267$, and $F = 363.0$. There were three outliers to eq 14, as shown in Table 1; the residuals for these range from 0.8 to 1.0 log units, that is, from three to four SD values. We can find no particular reason for these compounds to be outliers but note that any regression equation will almost always throw up statistical outliers. To assess the predictive capability of eq 14, we divided the data set into two halves—a training set used to construct another equation and a test set, not used at all in the construction, to test the predictions from the training equation. In order that the training set and the test set should cover the same area of chemical space, we used the Kennard–Stone method (31) to select the sets. The training equation, eq 15, is comparable to the full equation.

$$\log K_{\text{mus}} = -1.061 + 0.427E + 0.982S + 3.328A + 2.557B + 0.387L \quad (15)$$

where $N = 57$, $R^2 = 0.947$, $SD = 0.262$, and $F = 180.8$. When the training equation was used to predict the remaining 57 compounds in the test set, we found that $AE = -0.043$, $AAE = 0.236$, $SD = 0.306$, and $RMSE = 0.304$ log units. Thus, the training equation, and by implication eq 14, can predict values of $\log K_{\text{mus}}$ to about 0.2–0.3 log units, not far from our estimate of the measurement error.

Blood to Muscle Distributions for VOCs and Drugs. The combination of the $\log K_{\text{mus}}$ values in Table 1 with the known values for gas to blood distribution, as $\log K_{\text{blood}}$, yields values of the blood to muscle distribution coefficient for VOCs, as $\log P_{\text{mus}}$. These are given in Table 2. Application of eq 13 to the data yields eq 16. Although the SD value of 0.207 log units is a reasonable comparison with eqs 5–7 and 10, the correlation coefficient is poor and so is the F statistic. However, when we assessed the predictive capability of eq 16 by dividing the data into a training set and a test set each of 55 compounds, we found that the predictive capability of the training equation was quite good: $N = 55$, $AE = 0.037$, $AAE = 0.169$, $SD = 0.215$, and $RMSE = 0.213$ log units. R^2 for a plot of predicted values

Table 2. Calculation of log P_{muscle} from log K_{mus} and log K_{blood} for VOCs

solute	log K_{mus}^a	log K_{blood}^b	log P_{mus}^c	solute	log K_{mus}^a	log K_{blood}^b	log P_{mus}^c
(CF ₃) ₂ CHOCH ₂ F (sevoflurane)	0.22	-0.20	0.42	dichloromethane	0.79	1.12	-0.33
1,1,1,2-tetrachloroethane	1.60	1.55	0.05	diethyl ether	0.87	1.11	-0.24
1,1,1-trichloroethane	0.67	0.63	0.04	difluoromethane	0.16	0.20	-0.04
1,1,2,2-tetrachloroethane	2.00	2.13	-0.13	divinyl ether	0.34	0.41	-0.07
1,1,2-trichloroethane	1.36	1.67	-0.31	ethanol	3.08	3.27	-0.19
1,1-dichloroethane	0.71	0.88	-0.17	ethyl acetate	1.84	1.90	-0.06
1,1-dichloroethylene	0.31	0.70	-0.39	ethyl tert-butyl ether	1.35	1.07	0.28
1,1-dichloro-1-fluoroethane	0.02	0.32	-0.30	tert-butanol	2.80	2.68	0.12
1,2-dibromoethane	1.66	2.08	-0.42	methyl tert-butyl ether	1.57	1.18	0.39
1,2-dichloroethane	1.37	1.39	-0.02	tert-amyl methyl ether	1.38	1.22	0.16
1,2-dichloropropane	1.08	1.14	-0.06	tert-amyl alcohol	2.59	2.59	0.00
1,3-butadiene	-0.06	0.09	-0.15	ethylbenzene	1.41	1.47	-0.06
1,2-epoxy-3-butene	1.66	1.97	-0.31	ethylene oxide	1.75	1.80	-0.05
1-bromo-2-chloroethane	1.40	1.60	-0.20	ethylene	-0.20	-0.53	0.34
1-butanol	2.95	3.08	-0.13	fluorochloromethane	0.39	0.71	-0.32
1-chloropropane	0.32	0.59	-0.27	helium	-1.93	-2.00	0.07
1-nitropropane	1.46	2.31	-0.85	heptane	0.85	0.50	0.35
2-nitropropane	1.46	2.23	-0.77	hexachloroethane	1.88	1.76	0.12
3-methylpentane	0.58	-0.37	0.95	hexane	0.58	0.21	0.37
1-pentanol	2.91	2.83	0.08	hydrogen	-1.76	-1.77	0.01
1-propanol	2.95	3.06	-0.11	isobutyl acetate	2.04	1.69	0.35
2,2-dimethylbutane	0.00	-0.59	0.59	isopentyl acetate	2.32	1.79	0.53
2,2-dichloro-1,1,1-trifluoroethane	0.39	0.61	-0.22	isopropyl acetate	1.85	1.55	0.30
2-chloropropane	0.31	0.32	-0.01	isopropyl bromide	0.61	0.64	-0.03
2-heptanone	2.33	2.33	0.00	krypton	-1.38	-1.22	-0.16
2-methyl-1,3-butadiene	0.26	0.10	0.16	MeOCF ₂ CHCl ₂	1.35	1.28	0.07
2-methyl-1-propanol	2.74	2.92	-0.18	methane	-1.41	-1.42	0.01
2-methylpentane	0.46	-0.39	0.85	methyl acetate	1.81	1.98	-0.17
2-pentanone	2.00	2.14	-0.14	methyl chloride	-0.01	0.31	-0.32
2-propanol	2.87	3.02	-0.15	methylcyclopentane	0.70	-0.07	0.77
3-methyl-1-butanol	2.90	2.75	0.15	m-methylstyrene	2.26	2.28	-0.02
3-methylhexane	1.04	0.11	0.93	m-xylene	1.62	1.59	0.03
4-Methyl-2-pentanone	1.81	1.96	-0.15	nitrous oxide	-0.43	-0.34	-0.09
propanone	2.21	2.36	-0.15	o-xylene	1.71	1.42	0.29
acetylene	0.03	-0.06	0.09	pentachloroethane	1.86	2.02	-0.16
allyl chloride	1.04	1.24	-0.20	pentane	-0.15	-0.29	0.14
argon	-1.64	-1.52	-0.12	pentyl acetate	2.36	1.98	0.38
benzene	1.11	1.05	0.06	p-methylstyrene	2.26	2.37	-0.11
bromochloromethane	1.05	1.21	-0.16	propyl acetate	1.93	1.88	0.05
butan-2-one	2.14	2.24	-0.10	propyl bromide	0.62	0.97	-0.35
butyl acetate	2.20	1.94	0.26	propene	-0.27	-0.21	-0.06
carbon tetrachloride	0.66	0.62	0.04	p-xylene	1.58	1.61	-0.03
1-chloro-2,2-difluoroethylene	0.00	0.06	-0.06	radon	-0.81	-0.39	-0.42
CF ₃ BrClH (halothane)	0.74	0.57	0.17	styrene	1.67	1.67	0.00
CF ₃ BrFH	0.34	-0.22	0.56	sulfur hexafluoride	-1.85	-2.17	0.32
2-chloro-1,1,1-trifluoroethane	0.22	0.14	0.08	tetrachloroethylene	1.30	1.19	0.11
CF ₃ CH ₂ OCH=CH ₂	0.35	0.15	0.20	toluene	1.49	1.14	0.35
CHF ₂ OCF ₂ CHFCI	0.64	0.35	0.29	trans-1,2-dichloroethylene	0.55	0.88	-0.33
CHF ₂ OCHClCF ₃	0.31	0.20	0.11	trichloroethene	1.13	1.14	-0.01
chlorobenzene	1.53	1.63	-0.10	vinyl bromide	0.35	0.49	-0.14
chlorodibromomethane	1.75	1.88	-0.13	vinyl chloride	0.32	0.17	0.15
chloroethane	0.51	0.49	0.02	1,1-difluoroethylene	-0.54	-0.74	0.20
chloroform	1.12	1.15	-0.03	xenon	-1.00	-0.85	-0.15
cis-1,2-dichloroethylene	0.78	1.16	-0.38	2,3,4-trimethylpentane ^d	0.64	0.57	0.07
cyclohexane	0.52	0.17	0.35	octane ^d	0.93	0.68	0.25
cyclopropane	-0.31	-0.21	-0.10	2,2,4-trimethylpentane ^d	0.52	0.23	0.29
dibromomethane	1.61	1.87	-0.26				

^a From Table 1. ^b From ref 24. ^c From the previous two columns. ^d Not used.

from the training equation against observed values in the test set is noted; we find $R^2 = 0.537$, the same as for eq 16. From the test set statistics, eq 16 could be used to predict in vitro values of blood to muscle distributions for VOCs to about 0.22 log units.

$$\log P_{\text{mus}} (\text{in vitro}) = -0.185 - 0.209E - 0.593S - 0.081A - 0.168B + 0.741V \quad (16)$$

where $N = 110$, $R^2 = 0.537$, $SD = 0.207$, and $F = 24.1$.

The rather poor statistics of eq 16 are due, at least in part, to the small spread of observed values of log P_{mus} (in vitro), only 1.8 log units as compared to 5.0 log units for log K_{mus} . One

way to increase the range of values is to combine the in vitro data on VOCs with the in vivo data on drug molecules. To this end, we have collected data (22, 23, 32–46) on distribution from blood or plasma to muscle for drugs; see Table 3. We reference the blood or plasma data separately, even though we have shown that for distribution to the brain the two sets of data can be combined. It is impossible to compare the two sets of distribution to muscle directly, because there is only one compound, midazolam, for which we have both values. We therefore analyzed the data exactly as we did for distribution to the brain, including both blood to muscle and plasma to muscle distributions, and we denote this as $P_{\text{bp-mus}}$, the combined set

Table 3. Values of Distribution from Blood or Plasma to Muscle for Drugs

solute ^a	I	phase	ref	Log P_{mus}
3,3',5,5'-tetrachlorobiphenyl*	0	blood	41	0.00
4-chlorobiphenyl*	0	blood	42	0.00
4,4'-dichlorobiphenyl	0	blood	42	0.30
2,2',4,5,5'-pentachlorobiphenyl	0	blood	42	0.00
2,2',4,4',5,5'-hexachlorobiphenyl	0	blood	42	0.60
5-methyl-5-ethyl barbituric acid*	0	plasma	36	-0.22
5-ethyl-5-ethyl barbituric acid	0	plasma	36	-0.09
5-propyl-5-ethyl barbituric acid	0	plasma	36	0.14
5-butyl-5-ethyl barbituric acid	0	plasma	36	0.12
5-pentyl-5-ethyl barbituric acid	0	plasma	36	0.29
5-hexyl-5-ethyl barbituric acid*	0	plasma	36	0.31
5-heptyl-5-ethyl barbituric acid	0	plasma	36	0.16
5-octyl-5-ethyl barbituric acid	0	plasma	36	-0.09
5-nonyl-5-ethyl barbituric acid	0	plasma	36	0.10
AI-2 (SCH442416)*	0	blood	32	-0.05
AI-6*	0	plasma	38	0.43
biperiden*	0	plasma	22, 35	0.49
cocaine*	0	plasma	37	0.60
cefazolin*	1	plasma	22, 35	-0.94
clobazam*	0	plasma	22	0.41
cotinine*	0	plasma	22	-0.05
daidzein	0	blood	44	0.08
diazepam*	0	plasma	22, 23	0.15
2,3-dideoxyinosine (didanosine)*	0	plasma	22	-0.16
digoxin*	0	plasma	22	0.15
dicloxacillin*	1	plasma	22, 35	-1.30
fentanyl	0	plasma	22, 35	0.49
fluoxetine*	0	plasma	46	0.44
flurazepam*	0	plasma	22	0.69
glycyrrhetic acid*	1	plasma	22	-1.00
hexobarbital*	0	plasma	22, 35	-0.11
medazepam	0	plasma	22	0.34
methotrexate*	1	plasma	39	-0.82
midazolam*	0	plasma	33, 34, 40	0.11
midazolam	0	blood	34	0.08
morphine*	0	plasma	35	0.40
nalidixic acid*	1	plasma	35	-0.44
nicotine*	0	plasma	22	0.19
o-ethoxybenzamide (AI-5)	0	plasma	22	-0.09
pentazocine*	0	plasma	22, 35	0.77
penicillin V*	1	plasma	22, 35	-1.22
5-ethyl-5-(1-methylbutyl)barbital	0	plasma	22	-0.10
phenobarbital	0	plasma	22, 35	0.06
phenytoin*	0	plasma	22, 35	-0.16
p-phenylbenzoic acid*	1	plasma	22, 35	-1.10
p,p'-dichlorodiphenyl sulfone*	0	blood	45	0.58
propranolol*	0	plasma	23	0.34
procainamide*	0	plasma	22, 35	0.49
prazepam	0	plasma	22	0.26
pyrene*	0	plasma	43	0.20
R-carvedilol*	0	plasma	35	-0.10
salicylic acid*	1	plasma	22, 35	-0.85
S-carvedilol	0	plasma	35	0.20
terbinafine*	0	plasma	40	0.00
tetracycline*	0	plasma	22	0.29
theophylline*	0	plasma	22	-0.22
thiopental (thiopentone)*	0	plasma	22, 35	-0.12
thioridazine*	0	plasma	46	0.26
thiobarbital	0	plasma	22	-0.22
valproic acid*	1	plasma	35	-0.80

^a Values marked with * are the training set; the rest are the test set.

of in vivo data. These values all refer to rat muscle and are for passive transport from blood or plasma to muscle.

In Table 3, we have data for 59 compounds or 60 data points if we take the two values for midazolam separately. Application of eq 13 leads to eq 17, where we denote the number of data points as ND and the number of compounds as NC.

$$\text{Log } P_{bp-mus} (\text{in vivo}) = 0.082 - 0.059E + 0.010S - 0.248A + 0.028B + 0.110V - 1.022Ia \quad (17)$$

where ND = 60, NC = 59, $R^2 = 0.745$, SD = 0.253, and F =

25.9. The independent variable, Ia, is one that has been used before for solutes that contain the carboxylic acid group and takes the value Ia = 1 for this group and Ia = 0 for all other solutes. The compounds with the Ia descriptor are shown in Table 3. We divided the 60 data points into a training set of 40 and a test set of 20, in the usual way, and then obtained eq 18 for the training set.

$$\text{Log } P_{bp-mus} (\text{in vivo}) = 0.179 - 0.093E - 0.022S - 0.206A + 0.086B + 0.086V - 1.054Ia \quad (18)$$

where ND = 40, NC = 40, $R^2 = 0.777$, SD = 0.285, and F = 19.1. For the 20 compounds in the test set, the training equation predicted log P_{bp-mus} with AE = 0.051, AAE = 0.169, SD = 0.213, and RMSE = 0.208 log units. There is therefore no bias in the predictions, and eq 18 and then eq 17 can predict further values to about 0.20 log units. Equation 17 appears to be the only equation set up for the correlation and prediction of in vivo values of passive distribution of drugs from blood or plasma to muscle.

Finally, we seek to combine the in vitro data on VOCs with the in vivo data on drugs, to obtain a more general equation. Inspection of the equation for VOCs and the equation for drugs, eqs 16 and 17, shows that the coefficients are visibly different. However, we can use eq 17 to predict log P_{mus} for the 110 VOCs and find AE = 0.13, AAE = 0.25, RMSE = 0.31, and SD = 0.31 log units. The good prediction suggests that the difference in the equation coefficients could be due to the two series of compounds inhabiting different areas of chemical space. We therefore combined the VOC and drug data but incorporated a new indicator variable, Iv, defined as Iv = 1 for the in vitro data and Iv = 0 for the in vivo data, exactly as we did before (26). The Iv term is statistically significant (T -test = -2.124, p value = 0.035), and the resulting equation is shown as eq 19. A training set was constructed as usual and resulted in eq 20.

$$\text{Log } P_{bp-mus} (\text{in vivo} + \text{in vitro}) = -0.101 - 0.101E - 0.080S - 0.254A + 0.041B + 0.233V - 1.005Ia - 0.140Iv \quad (19)$$

where ND = 164, NC = 163, $R^2 = 0.594$, SD = 0.220, and F = 32.7.

$$\text{Log } P_{bp-mus} (\text{in vivo} + \text{in vitro}) = 0.014 - 0.102E - 0.021S - 0.246A + 0.072B + 0.125V - 1.009Ia - 0.183Iv \quad (20)$$

where ND = 82, NC = 82, $R^2 = 0.697$, SD = 0.235, and F = 24.4. Equation 20 was then used to predict values for the 82 data points in the test set, resulting in AE = -0.023, AAE = 0.166, SD = 0.213, and RMSE = 0.212 log units. We suggest that eq 19 is the equation of choice to predict further values of either the in vitro or the in vivo data for passive distribution from blood or plasma to muscle. From the results of the training and test sets, eq 19 could predict further values to around 0.2–0.25 log units. Thus, even though the correlation coefficient and F statistic of eq 19 are not at all good, the equation yields very satisfactory predictions of blood/plasma to muscle distribution. There are no previous equations with which to compare eq 19. In setting up the full eq 19, we discarded a number of data points that were considerable outliers. These were 1-nitropropane, 2-nitropropane, 2-methylpentane, methylcyclopentane, 3-methylhexane, and 3-methylpentane, all of which had residuals larger than 0.7 log units. We have no explanation for these outliers—The compounds involved are quite straightforward. However, omission of these compounds does not alter

Table 4. SMILES Strings for Some Compounds

solute name	SMILES
3,3',5,5'-tetrachlorobiphenyl	<chem>c1cc(Cl)cc(Cl)cc1c2cc(Cl)cc(Cl)c2</chem>
4-chlorobiphenyl	<chem>c1ccc(cc1)c2ccc(Cl)cc2</chem>
4,4'-dichlorobiphenyl	<chem>Clc1ccc(cc1)c2ccc(cc2)Cl</chem>
2,2',4,4',5,5'-pentachlorobiphenyl	<chem>Clc1cc(c(cc1Cl)Cl)c2c(ccc(c2)Cl)Cl</chem>
2,2',4,4',5,5'-hexachlorobiphenyl	<chem>c1(cc(c(cc1Cl)Cl)Cl)c2c(cc(c(c2)Cl)Cl)Cl</chem>
5-nonyl-5-ethyl barbituric acid	<chem>CCCC1(CCCCCCCCCC)C(=O)NC(=O)NC1=O</chem>
AI-2 (SCH442416)	<chem>COc5ccc(CCCn1ncc2c1nc(N)n3nc(nc23)c4ccco4)cc5</chem>
AI-6	<chem>Nc1cc(Cl)c(cc1c2nn[nH]2)S(N)(=O)=O</chem>
JP-10	<chem>C3CC2C1CCC(C1)C2C3</chem>
cefazolin	<chem>Cc4nncc(SCC1=C(N3C(SC1)C(NC(=O)Cn2cnnn2)C3=O)C(O)=O)s4</chem>
digoxin	<chem>CC1OC(C(C(O)C1O)OC2C(O)CC(OC2C)OC8C(O)CC(OC7CCCC3(C)C(CCC4C3CC(O)C5(C)C(CCC45O)C6=CC(=O)OC6)C7)OC8C</chem>
dicloxacillin	<chem>Cc1onc(c1C(=O)NC3C2SC(C)(C)C(N2C3=O)C(O)=O)c4c(Cl)cccc4Cl</chem>
flurazepam	<chem>CCN(CC)CCN2C(=O)CN=C(c1cccc1F)c3cc(Cl)ccc23</chem>
medazepam	<chem>CN2CCN=C(c1cccc1)c3cc(Cl)ccc23</chem>
methotrexate	<chem>CN(Cc2cnc1nc(N)nc(N)c1n2)c3ccc(cc3)C(=O)NC(CCC(O)=O)C(O)=O</chem>
penicillin V	<chem>CC3(C)SC2C(NC(=O)COC1cccc1)C(=O)N2C3C(O)=O</chem>
phenobarbital	<chem>CCC1(C(=O)NC(=O)NC1=O)c2ccccc2</chem>
p,p'-dichlorodiphenyl sulfone	<chem>Clc1ccc(cc1)S(=O)(=O)c2ccc(cc2)Cl</chem>
procainamide	<chem>CCN(CC)CCNC(=O)c1ccc(N)cc1</chem>
prazepam	<chem>Clc4ccc3N(CC1CC1)C(=O)CN=C(c2ccccc2)c3c4</chem>
R-carvedilol	<chem>COc1cccc1OCCNCC(O)COC3cccc4[nH]c2ccccc2c34</chem>
S-carvedilol	<chem>COc1cccc1OCCNCC(O)COC3cccc4[nH]c2ccccc2c34</chem>
tetracycline	<chem>CN(C)C2C1CC4C(=C(O)C1(O)C(=O)C(=C2O)C(N)=O)C(=O)c3c(O)cccc3C4(C)O</chem>
thiobarbital	<chem>CCC1(CC)C(=O)NC(=S)NC1=O</chem>

the correlation equation very much. If they were retained, then eq 19 would have $ND = 170$, $NC = 169$, $R^2 = 0.534$, $SD = 0.257$, and $F = 26.5$.

We have not given structures for all of the various compounds, because these have nearly all been set out previously. In Table 4, we give SMILES notations for those compounds not before indicated. Also, we have not listed the descriptors for the compounds that we have dealt with for the same reason.

Conclusions

It is possible to obtain a reasonable fitting equation, eq 14, for air to muscle distributions for 114 VOCs and to show that such an equation is capable of predicting further values of $\log K_{mus}$ to about 0.2–0.3 units, not far, we suggest, from experimental error. An estimate of this can be obtained from our analysis of experimental data on human and rat muscle above. We found that $AE = -0.01$, $AAE = 0.256$, and $SD = 0.299$ log units. Because the systematic error (AE) is almost zero, the values of AAE and SD must reflect random experimental error of around 0.25–0.30 log units. Although equations can be set up for the passive distribution of VOCs or of drugs (separately) from blood/plasma to muscle, we suggest that a combined equation for a total of 163 compounds, eq 19, is the preferred equation. This equation is capable of predicting further values of $\log P_{bp-mus}$ (in vivo + in vitro) to within about 0.25 log units, again, which we suggest is not far from experimental error. The latter will include the experimental error in both $\log K_{blood}$ and $\log K_{mus}$ and hence cannot be less than the experimental error in $\log K_{mus}$ that we estimate as around 0.25–0.30 log units. Just as for distribution from blood/plasma/serum to brain, the combined equation requires an additional indicator variable for the VOCs.

We stress that our method of prediction of further values of $\log K$ or $\log P$ is quite different from fragment-based methods. To predict a value for a VOC or a drug by the latter method, the various structural fragments in the VOC or drug must be included in the fragment scheme. The list of VOCs in Table 1 does not contain any nitrile, and if a fragment-based scheme

was constructed from the data in Table 1, it would not be possible to predict a value of $\log K_{mus}$ for, say, acetonitrile. In our method, structural fragments are not used, but compounds are characterized by the descriptors in eqs 12 and 13. Thus, the requirement for prediction is that descriptors for a cnewc VOC are known and that they lie within the range of descriptors used to set up the relevant equation. It is not necessary for the structural features of the new VOC to be included in the database. For acetonitrile, the known descriptors are (27) $E = 0.237$, $S = 0.90$, $A = 0.07$, $B = 0.32$, and $L = 1.739$, and use of eq 14 yields a prediction of $\log K_{mus} = 1.48$ by simple arithmetic. The use of molecular descriptors instead of structural fragments greatly increases the number of possible predictions, and this is one advantage of a molecular descriptor scheme. Of course, any prediction based on data for passive transport, either using a fragment method or our descriptor method, will be a prediction for passive transport only.

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

References

- (1) Meulenberg, C. J. W., and Vijverberg, H. P. M. (2000) Empirical relations predicting human and rat tissue: Air partition coefficients of volatile organic compounds. *Toxicol. Appl. Pharmacol.* 165, 206–216.
- (2) Fiserova-Bergerova, V., and Diaz, M. L. (1986) Determination and prediction of tissue-gas partition coefficients. *Int. Arch. Occup. Environ. Health* 58, 75–87.
- (3) 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 liquid and tissues. *Toxicol. Appl. Pharmacol.* 98, 87–99.
- (4) 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.
- (5) 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.
- (6) Kaneko, T., Wang, P.-Y., and Sato, A. (2000) Partition coefficients for gasoline additives and their metabolites. *J. Occup. Health* 42, 86–87.

- (7) 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.
- (8) Nussbaum, E., and Hursh, J. B. (1957) Radon solubility in rat tissues. *Science* 125, 552–553.
- (9) 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.
- (10) 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.
- (11) 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.
- (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) Filser, J. G., Csanady, G. 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.
- (14) 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.
- (15) Csanady, G. A., Denk, B., Putz, C., Kreuzer, P. E., 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.
- (16) Csanady, G. 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.
- (17) Borghoff, S. J., Murphy, J. E., and Medinsky, M. A. (1996) Development of a physiologically based pharmacokinetic model for methyl tertiary-butyl ether and tertiary-butanol in male fischer-344 Rats. *Fundam. Appl. Toxicol.* 30, 264–275.
- (18) Balaz, S., and Luckacova, V. (1999) A model-based dependence of the human tissue/blood partition coefficients of chemicals on lipophilicity and tissue composition. *Quant. Struct.-Act. Relat.* 18, 361–368.
- (19) Zhang, H. (2004) A new nonlinear equation for the tissue/blood partition coefficients of neutral compounds. *J. Pharm. Sci.* 93, 1595–1604.
- (20) Rodgers, T., Leahy, D., and Rowland, M. (2005) Physiologically based pharmacokinetic modelling 1: Predicting the tissue distribution of moderate-to- strong bases. *J. Pharm. Sci.* 94, 1237–1248.
- (21) Rodgers, T., Leahy, D., and Rowland, M. (2005) Tissue distribution of basic drugs: Accounting for enantiomeric, compound and regional differences amongst β -blocking drugs. *J. Pharm. Sci.* 94, 1259–1276.
- (22) Poulin, P., and Theil, F.-P. (2000) A priori prediction of tissue: Plasma partition coefficients of drugs to facilitate the use of physiologically based pharmacokinetic models in drug discovery. *J. Pharm. Sci.* 89, 16–35.
- (23) Poulin, P., and Theil, F.-P. (2002) Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug distribution. *J. Pharm. Sci.* 91, 1358–1370.
- (24) Abraham, M. H., Ibrahim, A., and Acree, W. E., Jr. (2005) Air-to-blood distribution of volatile organic compounds: A linear free energy analysis. *Chem. Res. Toxicol.* 18, 904–911.
- (25) Abraham, M. H., Ibrahim, A., and Acree, W. E., Jr. (2006) Air to brain, blood to brain and plasma to brain distribution of volatile organic compounds: Linear free energy analyses. *Eur. J. Med. Chem.* In press.
- (26) Abraham, M. H., Ibrahim, A., and Acree, W. E., Jr. (2006) A database for partition of VOCs and drugs from blood/plasma/serum to brain, and an LFER analysis of the data. *J. Pharm. Sci.* In press.
- (27) Abraham, M. H. (1993) Scales of hydrogen bonding: Their construction and application to physicochemical and biochemical processes. *Chem. Soc. Rev.* 22, 73–83.
- (28) 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.
- (29) PharmaAlgorithms Inc. *PharmaAlgorithms, ADME Boxes*, Version 2.2, PharmaAlgorithms Inc., Toronto, Ontario, Canada.
- (30) Minitab Inc. (2003) *Minitab*, version 14, Minitab Inc., State College, PA.
- (31) Kennard, R. W., and Stone, L. A. (1959) Computer aided design of experiments. *Technometrics* 11, 137–148.
- (32) Fazio, F., Todde, S., Moresco, R. M., Simonelli, P., Baraldi, P. G., Cacciari, B., Spalluto, G., Varani, K., Monopoli, A., Matarrese, M., Carpinelli, A., Magni, F., and Kienle, G. K. (2000) Design, radio-synthesis, and biodistribution of a new potent and selective ligand for in vivo imaging of the adenosine A2A receptor system using positron emission tomography. *J. Med. Chem.* 43, 4359–4362.
- (33) Bjorkman, S., Wada, D. R., Berling, B. M., and Benoni, G. (2001) Prediction of the disposition of Midazolam in surgical patients by a physiologically based pharmacokinetic model. *J. Pharm. Sci.* 90, 1226–1241.
- (34) Bjorkman, S., Fyge, A., and Qi, Z. (1996) Determination of the steady-state tissue distribution of midazolam in the rats. *J. Pharm. Sci.* 85, 887–889.
- (35) Bjorkman, S. (2001) Prediction of the volume of distribution of a drug: Which tissue-plasma partition coefficients are needed. *Pharm. Pharmacol.* 54, 1237–1245.
- (36) Blakey, G. E., Nestorov, I. A., Arundel, P. A., Aarons, L. J., and Rowland, M. (1997) Quantitative structure-pharmacokinetics relationships: I. Development of a whole-body physiologically based model to characterise changes in pharmacokinetics across a homologous series of barbiturates in the rat. *J. Pharmacokinet. Biopharm.* 25, 277–312.
- (37) Bonate, P. L., Swann, A., and Silverman, P. B. (1996) Preliminary physiologically based pharmacokinetic model for cocaine in the rat: Model development and scale-up to humans. *J. Pharm. Sci.* 85, 878–883.
- (38) Lee, H. S., and Lee, M. G. (1995) Stability, tissue metabolism, tissue distribution and blood partition of azosemide. *Biopharm. Drug Dispos.* 16, 547–561.
- (39) Bischoff, K. B., Dedrick, R. L., Zaharko, D. S., and Longstreth, J. A. (1971) Methotrexate pharmacokinetics. *J. Pharm. Sci.* 60, 1128–1133.
- (40) McLachlan, A. J., and Hosseini-Yegabeh, M. (2001) Tissue distribution of terbinafine in rats. *J. Pharm. Sci.* 90, 1817–1828.
- (41) Tuey, D. B., and Mathews, H. B. (1977) Pharmacokinetics of 3,3',5,5'-tetrachlorobiphenyl in the male rat. *Drug Metab. Dispos.* 5, 444–450.
- (42) Lutz, R. J., Dedrick, R. L., Mathews, H. B., Eling, T. E., and Anderson, M. W. (1977) A preliminary pharmacokinetic model for several chlorinated biphenyls in the rat. *Drug Metab. Dispos.* 5, 386–396.
- (43) Haddad, S., Withey, J., Lapare, S., Law, F., and Krishnan, K. (1998) Physiologically based pharmacokinetic modeling of pyrene in the rat. *Environ. Toxicol. Pharmacol.* 5, 245–255.
- (44) Csanady, G. A., Oberste-Frielinghaus, H. R., Semder, B., Baur, C., Schneider, K. T., and Filser, J. G. (2002) Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein. *Arch. Toxicol.* 76, 299–305.
- (45) Parham, F. M., Mathews, H. B., and Portier, C. J. (2002) A physiologically based pharmacokinetic model of p,p'-dichlorodiphenyl sulfone. *Toxicol. Appl. Pharmacol.* 181, 153–163.
- (46) Wojcikowski, J., and Daniel, W. A. (2002) Thioridazine-fluoxetine interactions at the level of the distribution process in vivo. *Pol. J. Pharmacol.* 54, 647–654.

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