Correlation of tissue, blood, and air partition coefficients of volatile organic chemicals

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ABSTRACT The physical chemical factors controlling partition coefficients between air, water, blood, and various tissues are discussed. It is suggested that improved insights into the relations between partition coefficients, which are frequently expressed as correlations, may be obtained by viewing the partition coefficients as ratios of solubilities or pseudosolubilities. A simple, novel correlation approach is developed and applied to 24 volatile organic chemicals, which enables tissue/blood, tissue/air, and blood/air partition coefficients to be estimated from water solubility and vapour pressure. An illustration is presented in which these solubilities are used to calculate the equilibrium distribution of dichloromethane between air, blood, and various tissues.

Pharmacokinetic models have proved useful in predicting the concentration time course of drugs, anaesthetics, industrial solvents, and environmental contaminants in blood and biological tissue. They have been applied to the design of optimum drug or anaesthetic regimens, determination of the kinetics of industrial toxicants, and the relation between environmental levels of chemicals and their concentrations in human or animal tissue. They permit prediction of the physiological distribution of chemicals of similar properties, extrapolation of this distribution to other species, and aid in the interpretation of responses.

In these models it is essential to include reliable expressions for tissue/blood and blood/gas partitioning, as well as for physiological volume and kinetic parameters. Thus there is an incentive to develop methods to correlate and predict tissue/gas and blood/gas partition coefficients. Several studies have reported such correlations.¹⁻⁴

In the present paper we discuss and illustrate a novel approach for calculating and correlating partitioning characteristics. Rather than correlate partition coefficients, which are inherently functions of properties of the chemical in two phases—for example, tissue and blood or tissue and air—we treat each phase individually and assign and correlate a single "solubility" property to each chemical in each phase. The advantage of this approach is that it shows immediately how a partition coefficient is influenced by each contributing phase. Most important, it avoids

a problem of developing apparently significant correlations by inadvertently correlating a quantity with itself. It also leads to a simple method of calculating equilibrium concentrations and distributions of chemicals within an organism.

To illustrate the statistical problem, we consider a series of chemicals (subscripts 1, 2, 3) of limited solubility in water, fat, and a tissue (subscripts W, F, and T). The partition coefficients—for instance, K_{FW1} , the partition coefficient of chemical 1 between fat and water—may also be regarded as the ratio of the solubility S_{F1} and S_{W1} —that is, K_{FW1} is S_{F1}/S_{W1} . For example, a set of solubility data in arbitrary units may be:

$S_{F1} = 1000$	$S_{T1} = 300$	$S_{W1} = 100$
$S_{F2} = 900$	$S_{T2} = 250$	$S_{W2} = 10$
$S_{F3} = 800$	$S_{T3} = 280$	$S_{W3} = 1$

The corresponding partition coefficients are thus:

$K_{FW1} = 10$	$K_{TW1} = 3$	(S_{T1}/S_{W1})
$K_{FW2} = 90$	$K_{TW2} = 25$	
$K_{FW3} = 800$	$K_{TW3} = 280$	

Regression of K_{FW} with K_{TW} will show an apparently significant relation with K_{FW} approximately equal to $3.2 K_{TW}$. This correlation, however, is entirely the result of the presence of S_W in the denominator of both quantities. This water solubility varies by a factor of 100 whereas the fat and tissue solubilities are fairly constant and do not contribute significantly to the variation in partition coefficient between chemicals. This constancy is obscured when only partition coefficients are used since it is not immediately clear

which phase(s) contribute to the variation in the K values. The linear partition coefficient regressions may thus be distorted by containing three variables. Accordingly, we suggest that more insight into relations between partition coefficients may be gained by viewing each phase individually.

By this approach it is possible to deduce probable partition coefficients from water solubility alone—that is, where no partition coefficient data exist. For example, if a fourth structurally similar chemical in this series has a water solubility of 50, it may be estimated that its fat/water and tissue/water partition coefficients will be about 20 and 6 respectively.

Phase equilibria

We first set out the rigorous thermodynamic basis of phase equilibrium using fugacity as an equilibrium criterion, derive relations between fugacities, solubilities, and partition coefficients, and then illustrate the approach for a set of relatively volatile organic chemicals that are of pharmacokinetic interest. The thermodynamic background is reviewed by Prausnitz.⁵

When characterising the partitioning of an organic chemical between two phases such as water and fat, a partition coefficient K_{ij} is usually defined as the dimensionless concentration ratio C_i/C_j where C may have units such as g/l, mol/l or mol/m³. At equilibrium, the chemical potentials, activities, or fugacities of the solute are equal in each phase. An alternative method of expressing partitioning is to relate each concentration separately to a common chemical potential, activity, or fugacity. This latter approach has the advantage that it clearly divides the partition coefficient into the two separate contributions of each phase. It is particularly advantageous to use fugacity as the equilibrium criterion since it is approximately linearly related to concentration, whereas chemical potential is logarithmically related. To elucidate the relations between partition coefficients we discuss their fundamental relations to fugacity.

We adopt the approach here of defining for each chemical in each phase a solubility or "pseudosolubility" such that the partition coefficient between these two phases is the ratio of these solubilities.

For a gas phase, or air, the fugacity f Pa of a solvent is essentially equal to its partial pressure P Pa, the exceptions occurring when the solvent self-associates as in the case of NO₂ or carboxylic acids. The partial pressure is related to concentration in air C_A mol/m³ through the gas law as

$$C_A = P/RT = f/RT \quad (1)$$

where R is the gas constant 8.314 Pa m³/mol K and T is absolute temperature K. The maximum or saturation

solubility in air C_A^s occurs when P equals the vapour pressure P^s , and C_A^s equals P^s/RT . Solubilities in air may thus be determined readily from vapour pressure data.

For a liquid phase such as water the fugacity expressed as

$$f = x\gamma P^s$$

where x is the mole fraction of solvent, γ is an activity coefficient or correction factor for non-ideality, and P^s is the vapour pressure of the pure liquid chemical at the system temperature. This is essentially a statement of Raoult's Law, corrected if necessary with the factor γ . Now x is related to concentration by

$$C_L = x/v$$

where v is the molar volume of the liquid solvent (m³/mol) and is, for example, 18×10^{-6} m³/mol or 18 cm³/mol for water. Inherent in this equation is the assumption that the solute is present at a low enough concentration that it does not substantially affect the molar volume. From equations 2 and 3 it follows that the concentration is given by

$$C_L = f/(v\gamma P^s)$$

Now, at saturation conditions, the chemical's fugacity and vapour pressure are usually equal, thus the solubility of the chemical in the liquid is given by

$$C_L^s = 1/v\gamma$$

There are three methods of estimating C_L^s .

Firstly, for sparingly soluble liquids such as benzene in water the solubility may be measured directly. For example, benzene has a solubility in water of 1780 g/m³ or 22.8 mol/m³, thus γ is 2440 indicating a high degree of non-ideality in the water phase—that is, the benzene exerts a partial pressure 2440 times that suggested by Raoult's Law.

Secondly, information or correlations may be available on the magnitude of γ from vapour/liquid equilibrium or other measurements as reviewed, for instance, by Reid *et al.*⁶ For example, correlations are available for infinite dilution activity coefficients of alcohols in water.⁶ Thus for an alcohol of activity coefficient γ equal to 3 in water of molar volume 18×10^{-6} mol/m³, the solubility C_L^s is 18 500 mol/m³. In reality, the alcohol is miscible with water and no solubility may be determined experimentally. C_L^s is thus a pseudosolubility which may only be calculated, not measured directly.

The third method uses air/liquid partition data in the form of gas solubilities or Henry's law constants. For complex liquids there is often doubt about γ and it may be convenient to combine them and P^s into a single quantity H the Henry's law constant H Pa mol expressed as

$$H = P/C = f/C = v\gamma P^s \quad (6)$$

Thus

$$C = f/H \quad (7)$$

If we assume that H is not only P/C but also P^s/C^s the ratio of the saturation vapour pressure to the solubility in the liquid C_L^s mol/m³, then

$$C_L^s = P^s/H \quad (8)$$

For this method a vapour pressure and a Henry's law constant are required. The latter may be in the form of a gas/liquid or gas/tissue partition coefficient (equivalent to H/RT) or an Ostwald or Bunsen gas solubility coefficient.

Complex liquids or solid/liquid mixtures are conveniently treated as additive volumes of different components. For example, blood may be treated as a mixture of water, lipid, protein, and other components. If each component is assigned separate properties and an effective volume fraction y the bulk properties of the mixture, such as C^s , may be expressed as the sum of that of the components,

$$C^s = y_1 C_1^s + y_2 C_2^s + \text{etc} = \Sigma y_i C_i^s \quad (9)$$

Having established these individual solubility relations, the various partition coefficients may be deduced as follows

Liquid/air—for example, water/air or oil/air

$$K = C_L/C_A = (f/(v\gamma P^s))/(f/RT) = RT/v\gamma P^s = C_L^s RT/P^s \quad (10)$$

K may be regarded as the ratio of solubility in the liquid C_L^s to solubility in air C_A^s or P^s/RT .

Liquid/liquid—for example, oil/water

$$K = C_{L1}^s/C_{L2}^s = v_2\gamma_2/v_1\gamma_1 \quad (11)$$

Clearly the reason that a solute such as benzene has such a high oil/water partition coefficient is that it has a low solubility in water C_{L2}^s due to its large activity coefficient γ_2 in water. Its solubility in oil C_{L1}^s is relatively large and γ_1 , relatively small (say, 3) reflecting the near ideality of the mixture of organic solvent in an organic medium.

Complex liquid/air—for example, blood/air

$$K = C_c/C_A = \Sigma [y_i C_{Li}^s]/C_A = (RT/P^s) \Sigma [y_i C_{Li}^s] = \Sigma [y_i (C_{Li}^s RT/P^s)] = \Sigma [y_i K_{Li}] \quad (12)$$

where K_{Li} is the component/air partition coefficient.

Complex liquid/liquid—for example, blood/fat

$$K = C_c/C_L = \Sigma y_i C_{Li}^s/C_L^s = v_L\gamma_L \Sigma [y_i C_{Li}^s] = \Sigma [y_i (\gamma_L v_L/\gamma_i v_i)] = \Sigma [y_i K_{Li}] \quad (13)$$

For a complex liquid the bulk partition coefficients are thus expected to be additive in proportion to the volume fractions of the contributing phases.

When correlating partition coefficients we suggest that it is preferable to examine the individual phase

solubilities or pseudosolubilities rather than their ratios because, as was discussed earlier, two variables x and y which are unrelated may appear to be related if plotted as x/z versus y/z . Fat/air and muscle/air partition coefficients appear to be related because both contain the air solubility. It is preferable to examine a chemical's fat solubility and muscle solubility separately and independently of their common air solubility.

A common surrogate for organic phases is *n*-octanol and extensive data exist for *n*-octanol-water partition coefficients K_{ow} of solvents.⁷ Recently Miller *et al* have shown that this partition coefficient is primarily controlled by water solubility, with a contribution from solute molar volume.⁸ It is thus possible to estimate K_{ow} from aqueous solubility. If a water solubility or pseudosolubility is available a solubility or pseudosolubility in octanol may be estimated as $K_{ow}C_L^s$, by assuming that K_{ow} is not only the ratio of concentrations but also the ratio of solubilities. Other less defined organic liquids such as olive oil may also be used for this purpose.

In summary, equations have been presented expressing fugacity, solubility, and partition coefficients in terms of the fundamental thermodynamic quantities γ , P^s , C^s , and molar volumes v for simple phases with a further dependence on volume fractions y for complex phases. We now examine the partition coefficients reported in publications and deduce the values of the fundamental phase solubilities, hoping that these solubilities may be individually predictable. Subsequently, we illustrate how these solubilities may be used to predict equilibrium concentrations.

Data analysis

Table 1 gives the physical chemical properties of 24 volatile organic chemicals including the actual or pseudosolubilities in water, the saturation concentration or solubility in air (P^s/RT), and the pseudosolubility in octanol $K_{ow}C^s$. The water solubilities have been obtained either from data^{8 10 11 13} or calculated from activity coefficients⁹ or Oswald coefficients¹⁵ as described earlier.

Table 2 gives values of selected tissue/air and blood/air partition coefficients for these chemicals.^{1-3 16} By combining the partition coefficients and the air solubilities, solubilities in blood and various tissues may be calculated for each compound (table 3).

Results and discussion

It is striking that the water solubilities in table 1 range from 0.006 to 27 000 mol/m³, a factor of 4.5 million. The air solubilities vary from 0.7 to 42, a factor of only 60. The octanol solubilities vary from 700 to 6000,

Table 1 Physical chemical properties of 24 volatile organic chemicals at 37°C except for alkane solubilities which are at 25°C.⁷⁻¹⁴ The solubilities were obtained as indicated in the last column from data (E),^{8,10,11,13} activity coefficient correlations (A),⁹ or from Ostwald coefficients (O)¹⁵

Compound	Mol wt (g/mol)	Water sol'y C (mol/m ³)	Log K _{ow}	Vapour pressure (Pa)	Air sol'y VP/RT (mol/m ³)	Octanol sol'y K _{ow} C	Sol'y method
Methanol	32.04	26581	-0.82	30754	11.93	4023	A
Ethanol	46.07	7913	-0.32	15307	5.94	3787	A
2-Propanol	60.10	4200	-0.16	11670	4.53	2906	A
1-Propanol	60.10	5352	0.34	5847	2.27	11709*	A
Isobutanol	74.10	1282	0.65	3600	1.40	5726*	A
2-Butanone	72.10	2300	0.26	23330	9.05	4185	O
Acetone	58.08	6540	-0.24	50350	19.54	3763	O
n-Pentane	72.15	0.565	3.62	105000	40.74	2355	E
2, 2, Dimethyl butane	86.17	0.246	3.82	66100	25.6	1625	E
2 Methylpentane	86.17	0.166	4.28	45300	17.6	3163	E
n-Hexane	86.17	0.143	4.11	33200	12.9	1842	E
Methylcyclopentane	84.16	0.499	3.66	30100	11.7	2281	E
Cyclohexane	84.16	0.706	3.44	21800	8.46	1944	E
3-Methylhexane	100.21	0.034	4.77	14200	5.51	2016	E
n-Heptane	100.20	0.027	4.66	10800	4.19	1213	E
Octane	114.23	0.006	5.20	3560	1.38	916*	E
Benzene	78.11	23.20	2.13	21500	8.34	3130	O
Toluene	92.10	5.94	2.65	6860	2.66	2653	O
Styrene	104.14	3.5	2.95	1900	0.75	3128	O
Dichloromethane	84.93	256.50	1.25	91800	35.61	4561*	O
Chloroform	119.38	63.87	1.97	42200	16.37	5961*	O
1, 1, 1, Trichloroethane	133.41	9.7	2.49	26900	10.44	2998*	O
Trichloroethylene	131.50	10.2	2.29	16900	6.56	1989	O
Diethylether	74.12	610	0.77	110000	42.68	3592	O

only a factor of 8.6. It is suspected that the octanol solubilities are more constant than is indicated. If six suspect values (indicated by asterisks) are removed, the mean solubility in octanol is 2750 mol/m³ with 75% of the chemicals lying in the range 2000–4000 mol/m³.

To a first approximation, the octanol solubilities may be considered constant, especially when considered by comparison with the water and air

solubilities. The oil and fat solubilities in table 3 are fairly constant with mean values of 3000 and 2000 mol/m³ respectively. They are thus similar to the solubilities in octanol. The solubility in fat may be considered to be about 73% of the solubility in octanol. The mean solubility in oil which is slightly larger than that in octanol in this case will vary with the type of oil used. Octanol and oil are thus good surrogates for fat when attempting to predict

Table 2 Reported tissue/gas partition coefficients for the 24 chemicals^{1-3, 16}

	Oil	Blood	Liver	Kidney	Brain	Fat	Muscle	Heart	Lung
Methanol		2874		1355	1413	231	1309		1733
Ethanol		2516		940	1044	215	850		1172
2-Propanol		1426		503	560	180	502		590
1-Propanol		955		686	720	296	678		817
Isobutanol		896		371	387	388	343		400
2-Butanone		215		107	111	162	103		103
Acetone	86	330		146	148	86	151		160
n-Pentane	47	0.38	2.1	0.6	2.2	39.6	0.7	0.2	0.5
2, 2, Dimethyl butane	71	0.26	3.5	1.4	2.8	66	1.0	0.5	0.6
2 Methylpentane	103	0.41	4.5	2.0	3.8	87	2.9	1.4	0.8
n-Hexane	146	0.80	5.2	3.0	5.0	104	5.0	2.8	1.0
Methylcyclopentane	202	0.86	7.8	4.7	7.3	176	5.0	1.9	1.7
Cyclohexane	293	1.3	10.8	7.2	10.7	260	10.5	5.8	2.7
3-Methylhexane	311	1.3	10.6	7.3	10.2	277	10.8	5.3	
n-Heptane	452	1.9	10.8	8.9	12.4	385	12.5	6.1	2.5
Octane			26	8.2	16.5	233	8.6	18	5.0
Benzene	492	7.8	23	12	18	425	16	17	12
Toluene	1471	15.6	48	18	36	962	35	30	21
Styrene		52	140			2600	52		
Dichloromethane	152	9.7	7.2	5.8	6.0	85	4.8	7.0	5.8
Chloroform	401	10.30	17	11	20	280	12	8	7
1, 1, 1, Trichloroethane	356	38.60	17	6.7	8.3	251	6.7	9.0	4.7
Trichloroethylene	718	9.50	29	15	21	569	19	20	14
Diethylether	65	12.00	11	10	12	50	10	12	15

Table 3 Calculated solubilities or pseudosolubilities (mol/m^3) of the chemicals in various tissue groups using data in tables 1 and 2

	Oil	Blood	Liver	Kidney	Brain	Fat	Muscle	Heart	Lung
Methanol		34294		16169	16861	2756	15620		20679
Ethanol		14943		5583	6200	1277	5048		6961
2-Propanol		6457		2278	2536	815	2273		2672
1-Propanol		2167		1556	1633	672	1538		1853
Isobutanol		1252		518	541	542	479		559
2-Butanone		1946		969	1005	1466	932		932
Acetone	1680	6447		2852	2891	1680	2950		3126
n-Pentane	1915	15.5	85.6	24.4	89.6	1613	28.5	8.15	20.4
2, 2, Dimethyl butane	1821	6.7	89.8	35.9	71.8	1693	25.6	12.8	15.4
2 Methylpentane	1810	7.2	79.1	35.2	66.8	1529	51.0	24.6	14.1
n-Hexane	1881	10.3	67.0	38.6	64.4	1340	64.4	36.1	12.9
Methylcyclopentane	2359	10.0	91.1	54.9	85.3	2055	58.4	22.2	19.9
Cyclohexane	2478	11.0	91.4	60.9	90.5	2199	88.8	49.1	22.8
3-Methylhexane	1713	7.2	58.4	40.2	56.2	1526	59.5	29.2	
n-Heptane	1894	8.0	45.3	37.3	52.0	1613	52.4	25.6	10.5
Octane		9.48	35.9	11.3	22.8	322	11.9	24.9	6.9
Benzene	4104	65.1	191.9	100.1	150.2	3545	133.5	141.8	100.1
Toluene	3915	41.5	127.8	47.9	95.8	2561	93.2	79.9	55.9
Styrene		38.9	104.8			1947	38.9		
Dichloromethane	5412	345.4	256.4	206.5	213.6	3027	170.9	249.2	206.5
Chloroform	6566	168.6	278.4	180.1	327.5	4585	196.5	131.0	114.6
1, 1, 1, Trichloroethane	3716	402.9	177.4	69.9		2620	69.9	93.9	49.1
Trichloroethylene	4708	62.3	190.2	98.4	137.7	3731	124.6	131.1	91.8
Diethylether	2774	512.2	469.5	426.8	512.2	2134	426.8	512.2	640.2

solubilities or partition coefficients.

Blood solubilities in table 3 range from 7 to 34 000 with two striking features. For water miscible chemicals such as the alcohols, the solubility in blood approximates that in water C_w^* indicating that there is a negligible contribution to solubility by partitioning into blood lipids. For sparingly soluble compounds such as the alkanes, the solubility in blood is between 0.3 and 1% of the alkane's solubility in fat, and greatly exceeds the solubility in water, indicating that partitioning of these chemicals in blood is mainly into a lipid-like phase. For these sparingly water soluble chemicals in table 3, the average blood solubility is 9.5 mol/m^3 . Thus the blood solubility S_b may be estimated from the water and octanol solubilities as

$$S_b = C_w^* + 9.5$$

or

$$S_b = C_w^* + 0.0035 S_0$$

where S_b , S_f , and S_0 represent solubility in blood, fat, and octanol respectively with units of mol/m^3 . If an octanol/water partition coefficient K_{ow} is available the blood solubility could also be estimated from

$$S_b = C_w^* (1 + 0.0035 K_{ow})$$

since S_0 is $C_w^* K_{ow}$.

Examination of the tissue group solubilities shows that they have characteristics of solubility in both water and fat with the water solubility controlling again for the alcohols and the fat solubility for the alkanes. There are some suspect values which we believe may be due to errors in published values of partition coefficients and physical chemical properties.

For each chemical a solubility in a tissue, S_T , may be calculated as

$$S_T = xS_0 + yC_w^*$$

The constant x may be calculated using average tissue solubility data for those chemicals of low water solubility. An average value of y may be obtained by substituting the above x in the above equation for the highly water soluble chemicals. Alternatively, linear regression may be used. This method was applied to obtain correlations for solubilities in kidney, liver, and brain.

It is interesting that when using this approach the aromatics display solubilities in blood that are consistently higher than those predicted. For example, for benzene, published blood solubilities (mol/m^3) are 65 compared with the predicted 34; for toluene, 41 against 16; and for styrene 39 against 14. This suggests an additional protein or other binding corresponding to a solubility increase of 30 mol/m^3 for these aromatics. The reported solubilities of benzene and toluene in kidney, liver, and fat are also larger than those predicted but not by such a constant amount as in the case of blood. This again could be due to protein binding.

In summary, the following correlation system is suggested.

From the reported vapour pressure P^* (Pa) the air solubility (P^*/RT) or C_A^* is calculated. From the actual water solubility, or an activity coefficient correlation, or a gas/water partition coefficient, a water solubility C_w^* is calculated.

The other assumed solubilities (mol/m³) are:

Octanol	$S_0 = 2750$
Oil	$S_{oil} = 3000$
Fat	$S_F = 2000$

The tissue solubilities may then be calculated as follows:

Kidney

$$S_K = 0.014S_0 + 0.51C_w^s = 38.5 + 0.51C_w^s$$

Liver

$$S_L = 0.028S_0 + 0.51C_w^s = 77 + 0.51C_w^s$$

Brain

$$S_X = 0.026S_0 + 0.51C_w^s = 71.5 + 0.51C_w^s$$

Blood

$$S_B = C_w^s + 0.0035S_0 = C_w^s + 9.5 = C_w^s(1 + 0.0035K_{ow})$$

If the chemical is aromatic 30 mol/m³ is added to the blood solubility.

Each partition coefficient is then calculated as the ratio of the corresponding solubilities. These partition coefficients when plotted as in figs 1 to 4 show the expected good correlation with those observed by other workers. Much of the apparent correlation in these figures is attributable to the presence of a common variable on each axis. There are four common outliers: 1, 1, 1 trichloroethane, trichloroethylene, chloroform, and 1-propanol. With the exception of trichloroethylene, these compounds were indicated in table 1 as having suspect octanol solubilities. These may be due to errors in the calculated water solubilities.

Figure 5 is a regression of correlated values of fat/blood and kidney/blood partition coefficients. The line corresponding to the regression is essentially a plot of $(38.5 + 0.51 C_w^s)/(9.5 + C_w^s)$ versus $2000/(9.5 + C_w^s)$ (except for the aromatics) which is nearly linear, extending from a limit on the left side of partition

Fig 1 Comparison of published and correlated values of blood/air partition coefficients (logarithmic scale).

Fig 2 Comparison of published and correlated values of kidney/air partition coefficients (logarithmic scale).

coefficients of 0.51 (kidney/blood) and 0 (fat/blood) for a chemical of infinite water solubility to a limit of $38.5/9.5$ or 4.0 (kidney/blood) and $2000/9.5$ or 211 (fat/blood) for a chemical of negligible water solubility. The intermediate points lie approximately on a straight line. The exceptions are the three aromatics, benzene, toluene, and styrene, whose solubilities in blood include a correction factor of 30 mol/m³.

The advantage of this approach is that it shows clearly the dominant determinants of partition coefficients. Usually it is water solubility or vapour pressure—that is, vapour pressure. Furthermore, for a chemical that is similar in nature to this group it is possible to estimate the partition coefficients from only a knowledge of vapour pressure and water solubility; no other partition coefficient is needed. The method may also help to elucidate the presence of unusually high solubilities or binding to protein or other material. Similar correlations could be developed for other groups of chemicals.

Fig 3 Comparison of published and correlated values of liver/air partition coefficients (logarithmic scale).

Fig 4 Comparison of published and correlated values of brain/air partition coefficients (logarithmic scale).

Improvements in the correlation could be made by developing more detailed expressions for blood and tissue solubilities taking into account the various solute-solvent interactions which apply. The solvato-chronic parameter approach described by Abraham *et al* is particularly promising.¹⁵ For example, the use of a single solubility in fat is almost certainly a naive assumption and improvements in the correlation could be obtained by expressing this solubility as a function of molecular properties such as molar volume or dipole moment. There is no substitute for accurate, measured partition coefficients but these measurements are difficult to make and data are often lacking for uncommon systems. It is believed that the approach described here provides a simple method of estimating partition coefficients and checking the reasonableness and consistency of published values. It identifies more clearly the factors which underlie partition coefficient correlations.

Application to calculations of equilibrium partitioning

Having established the relative solubilities in these

Fig 5 Regression of correlated values of fat/blood and kidney/blood partition coefficients.

phases, it is possible to use them to calculate equilibrium distributions of these chemicals. At equilibrium, the fugacity of the chemical is equal in each phase, as is the ratio of fugacity to vapour pressure f/P^s . But f/P^s is also the ratio of the concentration to the solubility in each phase and is the thermodynamic activity which may also be used as a criterion of equilibrium. If the concentration in one phase is known—for example, air—then the activity in that phase may be calculated as the ratio of concentration to solubility in air C_A^s or P^s/RT . At equilibrium, all other phases will have identical activities, thus their concentrations may be deduced. Algebraically, this is equivalent to using partition coefficients.

Furthermore, if phase or tissue volumes are known the absolute and relative amounts of chemical in each phase may be deduced as shown in table 4, which shows the equilibrium distribution of dichloromethane in someone exposed to a concentration of 100 ppm (volume). Dichloromethane has a partial pressure of 10.1 Pa or an air concentration of 0.0039 mol/m³ or 100 ppm at 37°C. Since the vapour pressure of dichloromethane is 91800 Pa, this corresponds to an activity of 0.00011. The concentration in each phase will then be 0.00011 times the solubility, and the amounts will be as shown in table 4. The calculated blood concentration agrees within a factor of three with the concentration of 1 mg/l reported by Anderson *et al*.¹⁷ The reported concentration is close to steady state but is not quite at steady state. The steady state concentration will be lower than the calculated equilibrium concentration because of metabolic conversions. The tissue concentrations thus adopt values controlled by the relative rates of metabolism and intake by inhalation.

A similar calculation for styrene at 80 ppm gives an equilibrium blood concentration of 19 mg/l which is a factor of 19 greater than the observed value. This large factor is due to the rapid metabolism of styrene. An equilibrium model such as this must be used with caution because the concentrations represent maximum achievable values. When metabolism is rapid, considerably lower concentrations occur. As metabolic saturation is approached, the equilibrium model becomes more reliable.

The calculation may also be done using another concentration as a basis. For example, if the blood concentration is known the activity may be deduced and the other concentrations estimated.

Finally, if a total amount of chemical (body burden) is known then the activity may be deduced from that amount M mol, as

$$M = \sum C_i V_i = \sum A_i S_i V_i = A \sum S_i V_i$$

or

$$A = M / \sum S_i V_i \text{ then } C_i = A S_i$$

where S_i is the phase solubility (mol/m³) and V_i the

Table 4 Calculation of equilibrium distribution of dichloromethane (DCM) at 1 atm (101325 Pa) and 37°C and an inhalation exposure of 100 ppm (vol)

Solubility in water	256.5 mol/m ³						
Vapour pressure	91800 Pa						
Air concentration	100 ppm (vol)						
Partial pressure or fugacity	101325×100						
	$\frac{10^6}{101325} = 10.1 \text{ Pa}$						
Activity	$A = 10.1/P^* = 10.1/91800 = 1.1 \times 10^{-4}$						
	Volume (m ³)	Solubility (mol/m ³)	Concentration (mol/m ³)	(mg/l)	Amount (mol)	(mg)	%
Blood	0.0054	266	0.029	2.5	0.00016	14	8.6
Fat	0.00747	2000	0.22	19	0.0016	140	85.9
Brain	0.0012	202	0.022	1.9	2.6×10^{-5}	2.2	1.3
Kidney	0.0003	169	0.019	1.6	5.7×10^{-6}	0.48	0.3
Liver	0.00332	208	0.023	1.9	7.6×10^{-5}	6.5	4.0
Total					0.0019	163.0	100.0

volume (m³). This is useful in exploring the likely concentrations which will result from uptake of a given amount of chemical.

Conclusions

A novel method has been suggested for estimating blood/air and tissue/blood partition coefficients from the physical chemical properties of a chemical. The approach is firstly to estimate the chemical solubilities or pseudosolubilities in water and air. The mean solubilities in octanol, fat, and oil and then various tissues may be calculated. Various partition coefficients may then be estimated as ratios of the appropriate solubilities. This approach avoids statistical difficulties associated with correlating a quantity with itself, and it helps to elucidate the source of variation in, and magnitude of, partition coefficients. The application of the method to calculating concentrations and amounts of chemical in various physiological compartments has been illustrated.

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