The prediction of blood-tissue partitions, water-skin partitions and skin permeation for agrochemicals.

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Abstract

BACKGROUND**:** There is considerable interest in blood-tissue distribution of agrochemicals and a number of workers have developed experimental methods for *in vitro* distribution. These methods involve the determination of saline-blood and saline-tissue partitions; not only are they indirect, but they do not yield the required *in vivo* distribution.

RESULTS: We set out equations for gas-tissue and blood-tissue distribution, for partition from water into skin and for permeation from water through human skin. Together with Abraham descriptors for the agrochemicals, these equations can be used to predict values for all these

processes. Our predictions compare favourably to experimental *in vivo* blood-tissue distribution where available. The predictions require no more than simple arithmetic.

CONCLUSIONS: The present method represents a much easier and much more economic method of estimation of blood-tissue partitions than does the method that uses saline-blood and saline tissue partitions. It has the additional advantages that it yields the required *in vi*vo partitions, and is easily extended to the prediction of partition of agrochemicals from water into skin, and permeation from water through skin

Keywords: LFER; Abraham descriptors; blood-tissue partition; air-tissue partition; water-skin partition: skin permeation

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1 INTRODUCTION

The method of gas-liquid chromatographic (GLC) headspace analysis is a well established procedure for the determination of thermodynamic properties of compounds [1, 2]. A compound is equilibrated between the gas phase and a condensed phase, and the concentration of the compound in the gas phase (the headspace) and the condensed phase determined by analytical GLC. The ratio of the two concentrations then gives the gas-condensed phase partition

coefficient, K_s. If the units of concentration in both phases are the same, say mol dm $^{-3}$, then K_s is dimensionless.

K_s = conc of compound in condensed phase (mol dm $^{-3}$) / conc. of compound in the gas phase (mol dm $^{-3}$) (1)

The GLC headspace method has been used regularly [3-6] to obtain *in vitro* gas-blood and gas-tissue partition coefficients for volatile organic compounds, VOCs. These are defined as organic compounds with boiling points below around 260^{o}C. Since it is rather impractical to determine the concentration of a compound in a biological tissue by GLC, a procedure particularly developed by Gargas et al. [5] has been used. A fixed amount of the compound is added to an empty vial and a vial containing the tissue. The headspace concentrations are determined by GLC and the concentration in the tissue obtained by difference. Meulenberg and Vijverberg [7] list numerous gas-tissue partition coefficients that have been determined in this way. Once K_s has been found for blood (K_{blo}) and a tissue (K_{tis}) for a given compound, then the corresponding blood-tissue partition coefficient, P_{tis} can be obtained from eq (2); C_{tis} and C_{blo} are the equilibrium concentrations in tissue and blood.

$$P_{tis} = K_{tis} / K_{blo} = C_{tis} / C_{blo} \quad (2)$$

One limiting factor in the GLC headspace method is the volatility of the compound. If a compound is too involatile, it may not be possible to obtain an accurate determination of the headspace concentration. In order to circumvent this difficulty, Jepson *et al.* [8] devised a novel method in which the tissue was equilibrated with saline, and saline-tissue partition coefficients

were obtained from the concentration of the compound in the equilibrated saline and tissue. In Table 1 are the average values reported by Jepson *et al.* [8] for a number of compounds.

Table 1 here

Artola-Garicano *et al.* [9] modified the method of Jepson by determining the compound concentrations using solid-phase microextraction. They reported log *P* values as from water to tissue, although their experimental description refers to an unspecified concentration of saline, rather than water. Their results were comparable to those of Jepson *et a*l. [8] as shown in Table 2. Artola-Garicano *et al.* [9] also calculated blood-tissue partitions using Eq 2, see Table 2, not only from their own results but also from the results of Jepson *et al.*, [8] although the latter did not actually calculate any blood-tissue partition coefficients.

Table 2 here

In view of the importance of tissue distribution of compounds of environmental use, it is not surprising that these have been obtained for a number of agrochemicals by Tremblay *et al.* [10] who used the solid-phase microextraction method. In Table 3 are given Tremblay *et al.'s* values of blood to tissue partition coefficients, as log P_{tiss}. Note that Table 3 of Tremblay *et al.* [10] is headed "tissue to blood", but the given values in their Table are blood to tissue as defined through eq (2). [11]

Table 3 here

Murphy *et a*l. [12] used a variant of the method of Jepson *et al.* [8] and equilibrated tissues and blood against propylene carbonate rather than against saline. Their results for estradiol and 2,3,7,8-

tetrachloro-p-dioxin, TCPD, are in Table 4. The method developed by Jepson *et al.* [8] is quite general and is not limited to VOCs. Indeed, the compounds studied by Tremblay *et al.* [10] included nonvolatile herbicides, insecticides and fungicides. It is very important to note that the procedure developed by Gargas et al., [5] by Jepson *et al.* [8] and by Tremblay *et al.* [10] yields values of K_{tiss} and P_{tiss} that are *in vitro* values. Thus all the values in Tables 1-4 are *in vitro* and not *in vivo* values

Table 4 here

We have previously used gas-blood and gas-tissue partitions to obtain equations for *in vitro* partition between isolated blood and tissue, and data from studies on rats to obtain equations for *in vivo* partitions. It seemed of interest to compare predictions from our *in vitro* and *in vivo* equations with the *in vitro* results set out in Tables 1-4. This is one of the aims of the present work. Although we had equations for blood-brain, [13-16] blood-muscle, [17] blood-fat, [18] blood-liver [19] blood-lung, [20] and blood-skin partitions, [21] we had no equations for blood-kidney and blood-heart partitions. We then collected both *in vivo* and *in vitro* data to derive the appropriate equations. We also had equations for human skin permeation and partition, that are of environmental interest, [22, 23] and equations for gas-olive oil and saline-olive oil that are needed for comparison, [24] as well as equations for gas-water. [25] Our final aim is to set out equations that can be used to calculate and to predict blood-tissue and water-skin partition coefficients and permeation from water through skin for agrochemicals.

2 METHODS

Our method makes use of the two linear free energy relationships, LFERS, [26, 27] eqns. (3) and (4).

$$\text{Log } P = c + eE + sS + aA + bB + vV \quad (3)$$

$$\text{Log } K = c + eE + sS + aA + bB + lL \quad (4)$$

Eqn. (3) is used when the dependent variable is a water-phase (or a saline-phase) partition coefficient, as log *P*, for a series of solutes in a given system. Eqn. (4) is used when the dependent variable is gas to phase partition, as log *K* .

The independent variables in eqns. (3) and (4) are the Abraham solute descriptors as follows. [26, 27] *E* is the solute excess molar refractivity in units of $(cm^3\ mol^{-1})/10$, *S* is the solute dipolarity / polarizability, *A* and *B* are the overall or summation hydrogen bond acidity and basicity, and *V* is the McGowan characteristic volume in units of $(cm^3\ mol^{-1})/100$. *L* is the gas-hexadecane partition coefficient at 298 K. The solute descriptors are obtained from a variety of experimental data, including water-solvent partition coefficients, solubilities in organic solvents, and chromatographic data, as detailed by us previously.[27, 28] Clarke and Mallon [29] have given a detailed description our entire method, including the determination of the Abraham solute descriptors. The coefficients in eqns. (3) and (4) are obtained by multiple linear regression analysis, and serve to characterize the system under consideration. These coefficients are listed in Table 5 for *in vitro* partition from gas to tissue and from blood (plasma) to tissue for volatile organic compounds in rats and humans, for *in vivo* partition from blood to tissue in rats for drugs, and for *in vitro* partition from water to skin in humans for drugs. In addition we include an important equation for *in vitro* permeation of compounds from water through human skin. We

note that all our equations refer to passive partition from blood to tissue, and as far as possible we have excluded compounds that exhibit active transport, including efflux mechanisms. Recent studies on *in vivo* partition have tended to use high performance liquid chromatography or gas liquid chromatography coupled to mass spectroscopic detection as the method of analysis, This procedure can detect the presence of metabolites and enables values of tissue distribution to be obtained for the parent compound. We include in Table 5 two equations for the important gas-water partition coefficient, *Kw*, as log *Kw*. One equation is cast in terms of eqn. (3) and the other equation in terms of eqn. (4). Water is the only solvent for which a satisfactory equation in terms of eqn. (3) can be obtained.

The *in-vivo* equations are constructed from data on known experimental blood-tissue partitions of drugs in rats. The experimental log *P* values for a given tissue are then correlated against the descriptors shown in eqn. (3) to yield equations with log *P* as the dependent variable, the various descriptors as the independent variables, and the coefficients as given in Table 5. This procedure has been described previously. [14-21] Once the coefficients for a given blood-tissue system are known (Table 5), they can be combined with the descriptors for a given compound to yield a prediction of the particular blood-tissue partition.

Table 5 here

Tissues for which we did not have equations for gas-tissue and blood-tissue are kidney and heart, and so we have used data on *in vitro* gas to tissue and gas to blood partitions for VOCs and *in vivo* blood to tissue data for drugs to obtain eqns (5) - (7) for kidney. Here and elsewhere *N* is the number of observations, ie solutes, *SD* is the regression standard deviation, *R* is the correlation coefficient and *F* is the F-statistic. The corresponding equations for heart are eqns. (8)

– (10). These equations, and those listed in Table 5, are quite general and include neutral (that is unionized) acids and bases. Indeed, the equations for log *P* for drugs include an extra descriptor, *Ic*, for carboxylic acids. The *in vitro* data that we used was taken from the literature [3-7, 30-36] as was the *in vivo* data. [37-60]

$$\text{Log } K_{kidney} \text{ (VOCs)} = -1.005 + 0.489\,E + 0.774\,S + 3.000\,A + 2.719\,B + 0.497\,\text{L} \qquad (5)$$

$N = 70$, $SD = 0.252$, $R^2 = 0.955$, $F = 273.5$

$$\text{Log } P_{kidney} \text{ (VOCs)} = -0.155 + 0.193\,E - 0.462\,S - 0.922\,A + 0.232\,B + 0.750\,V \qquad (6)$$

$N = 70$, $SD = 0.218$, $R^2 = 0.593$, $F = 18.6$

$$\text{Log } P_{kidney} \text{ (Drugs)} = 0.494 - 0.067\,E - 0.426\,S - 0.367\,A + 0.232\,B + 0.410\,V - 0.481\,Ic$$

$N = 110$, $SD = 0.460$, $R^2 = 0.474$, $F = 15.5$, PSD = 0.488 (7)

$$\text{Log } P_{kidney} \text{ (Drugs)} = 0.485 - 0.071\,\text{E} - 0.391\,\text{S} - 0.309\,\text{A} + 0.186\,\text{B} + 0.414\,\text{V} - 0.513\,\text{Ic}$$

$N = 124$, $SD = 0.448$ $R^2 = 0.462$, $F = 16.9$, $PSD = 0.474$

PRESS = 26.53, $Q^2 = 0.399$,

$$\text{Log } K_{heart} \text{ (VOCs)} = -1.199 + 0.185\,E + 0.596\,S + 2.951\,A + 2.450\,B + 0.589\,\text{L} \qquad (8)$$

$N = 31$, $SD = 0.159$, $R^2 = 0.981$, $F = 264.3$

$$\text{Log } P_{heart}\text{ (VOCs)} = -0.458 + 0.041\,E - 0.045\,S - 0.881\,A - 0.224\,B + 0.948\,V \quad (9)$$

$N = 31$, $SD = 0.194$, $R^2 = 0.719$, $F = 12.8$

$$\text{Log } P_{heart}\text{ (Drugs)} = 0.132 - 0.039\,E - 0.394\,S - 0.376\,A + 0.009\,B + 0.527\,V - 0.572\,Ic$$

$N = 89$, $SD = 0.453$, $R^2 = 0.512$, $F = 14.3$, PSD = 0.556 (10)

$$\text{Log } P_{heart}\text{ (Drugs)} = 0.194 - 0.067\,E - 0.313\,S - 0.334\,A + 0.025\,BS + 0.449\,V - 0.526\,Ic$$

$N = 107$, $SD = 0.404$, $R^2 = 0.496$, F = 16.4, PSD = 0.479

PRESS = 22.9626 R-Sq(pred) = 29.15%

In eqn. (5) to eqn. (10) the statistical fits are always better for processes involving the *in vitro* transfer of VOCs than for processes involving *in vivo* transfer of drugs. This reflects the relative ease of making *in vitro* measurements as compared to the difficulty of the *in vivo* measurements.

Abraham and Martins [22] set out an equation for the partition of 45 varied solutes between water and human *stratum corneum*, *SC*. We have updated the equation using more recent descriptors based on additional experimental data, as eqn. (11), and include the coefficients in Table 5. We can also combine the log P_{SC} values with log K_w values for partition from the gas phase to water to obtain log K_{SC} values for partition from the gas phase to (water saturated) SC. The corresponding equation is given as eqn. (12).

$$\text{Log } P_{SC}\text{ (Drugs/VOCs)} = 0.523 + 0.101\,E - 0.076\,S - 0.022\,A - 1.951\,B + 1.652\,V$$

$$N = 45,\ SD = 0.221,\ R^2 = 0.909,\ F = 77.7 \qquad (11)$$

$$\text{Log } K_{SC}\text{ (Drugs/VOCs)} = -0.254 + 0.311\,E + 2.230\,S + 3.705\,A + 2.925\,B + 0.243\,L$$

$$N = 45,\ SD = 0.201,\ R^2 = 0.999,\ F = 11842.9 \qquad (12)$$

Liu *et al*. [23] have developed an equation for permeation of solutes from water through human skin, as log K_p with K_p in cm s^{-1}, that refers not only to neutral species but to ionic species as well, eqn. (13). The latter include cationic species such as protonated amines for which a new descriptor J^+ is needed, and anionic species such as carboxylate anions for which a new descriptor J^- is needed. The importance of eqn. (13) is that it enables permeation through skin to be estimated as a function of the aqueous pH. The coefficients in Table 5 are those for permeation of neutral species.

$$\text{Log } K_p = -5.420 - 0.102\,E - 0.457\,S - 0.324\,A - 2.680\,B + 2.066\,V - 1.938\,J^+ + 2.548\,J^- \qquad (13)$$

3 RESULTS

Before attempting to assess the results shown in Tables 1-4 obtained by the saline partition procedure, it is of some importance to check the *in vitro* equations in Table 5 for gas-tissue and blood-tissue partitions using data obtained by the original method, [3-7] as developed by Gargas. [5] Mahle *et al*. [61] determined gas-tissue partition coefficients for six VOCs in blood, liver, kidney, fat, muscle and brain making a total of 36 log K_{tiss} values. We compared the 36 values for adult male rats with values calculated using the equations in Table 5 and found an average error (observed – calculated) AE = 0.08, an average absolute error AAE = 0.15, a root mean square error RMSE = 0.19 and a standard deviation SD = 0.19 log units. The various log *K* values for tissues and blood yield 30 log P_{tiss} values. Comparison with calculated values from the equations in Table 5 yield AE = 0.00, AAE = 0.11, RMSE = 0.14 and SD = 0.14 log units, so that our equations for *in vitro* partition of VOCs do, indeed, reproduce the observed quantities.

Although *in vitro* blood-tissue partition coefficients are useful, it is the *in vivo* partition coefficients that are of the most importance. Very few such data are available to test our LFER equations, but Crowell *et al*. [62] give *in vivo* partition coefficients for triadimefon and triadimenol, obtained from a pharmacokinetic analysis using rats. Observed and predicted log P_{tiss} values are in Table 6, the latter from the equations given in Table 5 and the compound descriptors listed in Table 7.

Table 6 here

For the eight sets of observed and predicted log P_{tiss} values in Table 6, AE = -0.14, AAE = 0.20, RMSE = 0.26 and SD = 0.27 log units. Given that there will be an associated error in the observed log P_{tiss} values, the small AE of -0.14 log units, and the total SD error of 0.27 log units, suggests that the *in vivo* equations in Table 5 do yield reasonable predictions of *in vivo* blood-tissue partitions.

Whether or not the *in vitro* partitions obtained from saline-blood and saline-tissue partitions are equivalent to *in vivo* blood-tissue partitions cannot be determined directly, because there are no experimental *in vivo* blood-tissue partitions for comparison. However, we know that our LFER equations, Table 5, provide reasonable predictions of *in vivo* blood-tissue partitions for triadimefon and triadimenol, see Table 6. Therefore, a comparison of our predictions of *in vivo* blood-tissue partitions with the *in vitro* partitions obtained from saline-blood and saline-tissue partitions will provide an estimate, albeit an indirect one, of the possible equivalence of *in vitro* partitions with *in vivo* partitions..

For the nine *in vitro* blood-tissue partition coefficients listed in Table 2 for lindane, parathion and paraoxon, and the eight blood-tissue partition coefficients listed in Table 4 for estradiol and TCPD, we find for the total seventeen partition coefficients that AE = 0.15 (observed - predicted), AAE = 0.31, RMSE = 0.39 and SD = 0.40 as between our predicted and the observed *in vitro* partitions. In Table 3 are values of *in vitro* log P_{tiss} values for 47 systems. We can predict all these 47 log P_{tiss} values and a comparison between our predicted and the observed *in vitro* partitions yields AE = -0.31 (observed - predicted), AAE = 0.39, RMSE = 0.47 and SD = 0.48 log units.

Thus our predicted log P_{tiss} values relate to observed *in vivo* log P_{tiss} values with AE = -0.11 and SD = 0.23, whereas they relate to the two sets of observed *in vitro* partitions with AE = 0.15 and SD = 0.40 or AE = -0.31 and SD = 0.48 log units. Our predicted values are much closer to the observed *in vivo* log P_{tiss} values than they are to the observed *in vitro* partitions obtained by the saline-tissue method. It should be noted that the *in vitro* blood-tissue partition coefficients in Tables 1-3 are derived from saline-blood and saline-tissue partition coefficients, and represent partitions between two components, blood and a tissue, that are not actually in contact with each other, whereas a true *in vivo* partition is between blood and the tissue in contact. Similar comments apply to the results of Murphy *et al*.[12] who used propylene carbonate instead of saline, Table 4.

Since our calculational procedure yields good predictions of the required *in vivo* log P_{tiss} in the case of triadimefon and triadimenol, we suggest that it is an easier and cheaper method of estimating blood-tissue partitions than the saline-tissue method, particularly as the latter only leads to *in vitro* values. The calculational procedure has additional advantages in that predictions for other systems can also be carried out. Graham *et al*. [60] have examined a number of methods of calculating tissue partitions and have suggested that *in-silico* methods can accurately predict *in vivo* partitions. Our findings are in agreement with this suggestion. More recent methods have considered tissues as compartments of water, lipid and protein and have set out equations for transfer into the various compartments. The resulting equations, however, become very complicated. [63, 64]

We give in Table 7 the required descriptors for the compounds we have discussed, and in Table 8 are the predictions we can make. As part of our analysis to obtain descriptors for

compounds, we automatically calculate the gas-water partition coefficient K_w defined through an analogous equation to eqn. (1); this is also given in Table 7. K_w is an extremely difficult physicochemical property to measure experimentally, and so a calculation of log K_w could be very useful. The coefficients in equations for log K_w are given in Table 5.

Table 7 here

Table 8 here

One restriction to application of our method is that the descriptors in eqn. (3) and eqn. (4) need to be obtained from various experimental data, as set out previously. [26-29] In the absence of any 'experimental' descriptors, it is possible to use the ACD software 'Absolv' [65] to calculate descriptors just from structure. These descriptors are given in Table 7 for triadimefon and for triadimenol, and the corresponding predictions of log P_{tiss} are in Table 8. The Absolv descriptors, calculated just from structure, lead to good predictions of the log P_{tiss} values, as shown in Table 6. The use of the Absolv calculated descriptors greatly extends our method – all that is needed to obtain descriptors and then to make predictions as in Table 8 is the structure of an agrochemical. There is one important advantage of using Absolv calculated descriptors, and that is that predictions can be made just from structure before a candidate agrochemical has even been synthesised. Of course, use of estimated descriptors will increase the error of any predicted value, but their use still provides an important prediction from structure.

We note, above, that in the construction of equations for *in vivo* blood-tissue partition, we excluded, as far as possible, compounds that partition by an active mechanism. Thus all our predictions will refer to passive partition. As an aside, we mention that if a prediction of a given

blood-tissue partition and an experimental value for the partition are considerably different, this may indicate some form of active partition. Indeed, predictions of passive partition can help to establish whether a particular compound undergoes partition by a passive process or by an active mechanism.

4 CONCLUSION

We have shown that it is possible to calculate blood-tissue partition coefficients for agrochemicals, as log P_{tiss}, using the LFERs, eqn. (1) and eqn. (2). The calculated log P_{tiss} values are in good agreement with experimental *in vivo* values, and we suggest the calculation of blood-tissue partition coefficients by our LFER method represents an easy and economic method of estimation of in vivo log P_{tiss} values.

In addition to the predictions already given in Table 8, once the descriptors in eqn. (1) and eqn. (2) have been obtained for a given agrochemical, it is also possible to predict values for numerous other processes. These include partition coefficients from water and the gas phase to a very large number of organic solvents [28] and from water and the gas phase to room temperature ionic liquids. [66] Clarke and Mallon [29] have listed Abraham descriptors for a number of agrochemicals; these descriptors can be combined with the equation coefficients given in Table 5 to obtain values for the various processes by simple arithmetic.

REFERENCES

1 Abraham MH, Substitution at saturated carbon. Part IX.. Free energies of transfer from methanol to aqueous methanol of tetraalkyltins and the transition states in the bimolecular substitution of tetraalkyltins by mercuric chloride. *J Chem Soc. A*, 1061-1068 (1971).

2 Abraham MH, Grellier PL and Mana J, Limiting activity coefficients of triethylamine in 30 solvents by a simple gas-liquid chromatographic method. *J Chem Thermodyn* **6**: 1175-1179 (1974).

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

4 Fiserova-Bergerova V and Diaz, ML, Determination and prediction of tissue-gas partition coefficients. *Int. Arch. Occup. Environ. Health* **58***:* 75-87 (1986).

5 Gargas ML, Burgess RJ, Voisard DE, Cason GH and Andersen ME, Partition Coefficients of Low-Molecular-Weight Volatile Chemicals in Various Liquids and Tissues. *Toxicol. Appl. Pharmacol* **98***:* 87-99 (1989).

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

7 Meulenberg CJW and Vijverberg HPM., Empirical relations predicting human and rat tissues: air partition coefficients of volatile organic compounds. *Toxicol Appl Pharmacol* **165**: 206-216 (2000).

8 Jepson GW, Hoover DK, Black RK, McCafferty JD, Mahle DA and Gearhart JM, A partition

coefficient determination method for nonvolatile compounds in biological tissues. *Fund App Toxicol* **22**: 519-524 (1994).

9 Artola-Garicano E, Vaoes WHJ and Hermans JLM, Validation of negligible depletion solid-phase microextraction as a tool to determine tissue/blood partition coefficients for semivolatile and nonvolatile organic compounds. Toxicol App Pharmacol **166**: 138-144 (2000).

10 Tremblay RT, Kim D and Fisher JW, Determination of tissue to blood partition coefficients for nonvolatile herbicides, insecticides and fungicides using negligible depletion solid-phase microectraction (nd-SPME) and ultafiltration. *J Toxicol Environ Health Part A* **75**: 288-298 (2012).

11 Personal communication from Dr Raphael Tremblay.

12 Murphy JR, Janszen DB and Gargas ML, An in vitro method for determination of tissue partition coefficients of non-volatile chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin and estradiol. *J Appl Toxicol* **15**: 147-152 (1995).

13 Abraham MH, Ibrahim A and Acree, Jr. WE, Air-to-blood distribution of volatile organic compounds: a linear free energy analysis. *Chem. Res Toxicol* **18**: 904- 911 (2005).

14 Abraham MH, Ibrahim A and Acree, Jr. WE, Air to brain, blood to brain and plasma to brain distribution of volatile organic compounds: linear free energy analysis. *Eur J Med Chem* **41**: 494-502 (2006).

15 Sprunger LM, Gibbs J, Acree Jr. WE and Abraham MH, Correlation of human and animal air- to-blood partition coefficients with a single linear free energy relationship model. *QSAR Comb S*ci **27**: 1130-1139 (2008).

16 Abraham MH, Ibrahim A, Zhao Y and Acree, Jr. WE, A data base for partition of volatile organic compounds and drugs from blood/plasma/serum to brain, and an LFER analysis of the data. *J Pharm Sci* **95**: 2091-2100 (2006).

17 Abraham MH, Ibrahim A and Acree, Jr. WE, Air to muscle and blood/plasma to muscle distribution of volatile organic compounds and drugs: linear free energy analysis. *Chem Res Toxicol* **19**: 801-808 (2006).

18 Abraham MH and Ibrahim A, Air to fat and blood to fat distribution of volatile organic compounds and drugs: linear free energy analyses. *Eur J Med Chem* **41:** 1430-1438 (2006).

19 Abraham MH, Ibrahim A and, Acree Jr. WE, Air to liver partition coefficients for volatile organic compounds and blood to liver partition coefficients for volatile organic compounds and drugs. *Eur J Med Chem* **42:** 743-751 (2007).

20 Abraham MH, Ibrahim A and Acree Jr. WE, Air to lung partition coefficients for volatile organic compounds and blood to lung partition coefficients for volatile organic compounds and drugs. *Eur J Med Chem* **43:** 478-485 (2008).

21 Abraham MH and Ibrahim A, Blood or plasma to skin distribution of drugs: a linear free energy analysis. *Int J Pharmaceutics* **329**: 129-134 (2007)

22 Abraham MH and Martins F, Human skin permeation and partition; general Linear Free-Energy Relationship analyses. *J Pharm Sci* **93**: 1508-1523 (2004).

23 Zhang K, Chen M, Scriba GKE, Abraham MH, Fahr A, and Lui X, Human skin permeation of neutral species and ionic species: extended linear free-energy relationship analysis. *J*

Pharm Sci **101**: 2034 -2044 (2012).

24 Sprunger LM, Acree, Jr. WE and Abraham MH, Mathematical correlations for gas-to-olive-oil, gas-to-saline solution, and saline solution- to-olive oil partition coefficients based on the Goss modified Abraham model. *QSAR Comb Sci* **27**: 890-900 (2008).

25 Abraham MH, Andonian-Haftvan J, Whiting GS., Leo A. and Taft RW, Hydrogen bonding. part 34: the factors that influence the solubility of gases and vapours in water at 298 K, and a new method for its determination, J Chem Soc Perkin Trans. 2, 1777-1791 (1994).

26 Abraham MH, Scales of hydrogen bonding: their construction and application to physicochemical and biochemical processes. *Chem Soc Revs* **22**: 73-83 (1993).

27 Abraham MH, Ibrahim A and Zissimos AM, The determination of sets of solute descriptors from chromatographic measurements. *J Chromatogr A*. **1037:** 29-47 (2004).

28 Abraham MH, Smith RE, Luchtefeld R, Boorem AJ, Luo R and Acree Jr WE, Prediction of solubility of drugs and other compounds in organic solvents. *J Pharm Sci* **99**: 1500-1515 (2010).

29 Clarke ED and Mallon LJ, in Modern Methods in Crop Protection Research, ed by Jeschke P, Kramer W, Schirmer L and Witschel M, Wiley-VCH Verlag GmbH &Co, 273-279 (2012).

30 Zahlsen K, Eide I, Nilsen, AM, Nisen, OG, Inhalation kinetics of C6 to C10 aliphatic, aromatic and naphthetic hydrocarbons in rat after repeated exposures. *Pharmacol Toxicol* **71**: 144-149 (1992).

31 Abraham MH, Weathersby PK, Solubility of gases and vapours in biological liquids and tissues. *J Pharm Sci* **83**: 1450-1455 (1994).

32 Borghoff SJ, Murphy JE, Medinsky MA, Development of a Physiological Based Pharmacokinetic Model for Methyl tertiary-Butyl Ether and tertiary-Butanol in Male Fischer-344 Rats. *Fund Appl Toxicol* **30**: 264-275 (1996).

33 Knaak JB, Smith LW, 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 (1998).

34 Csanady GyA, Denk B, Putz C**,** Kreuzer**,** Kessler W, Baur C, Gargas ML, Filser JGA, 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. *Toxicology and Applied Pharmacology* **165**: 1-26 (2000).

35 Filser JG, Schmidbauer R, Rampf F, Baur CM, Putz C, Csanady GA, Toxicokinetics of inhaled propylene in mouse, rat, and human. *Toxicol Applied Pharmacol* **169**: 40-51 (2000).

36 Kaneke T, Wang P-Y, Sato A, Partition coefficients for gasoline additives and their metabolites. *J Occup Health* **42**: 86-87 (2000).

37 Bischoff KB, Dedrick RL, Zaharko DS, Longstreth JA, Methotrexate pharmacokinetics, *J Pharm Sci* **60**: 1128-1133 (1971).

38 Schillings RT, Sisenwine SF, Ruelius HW, Disposition and metabolism of lorazepam in the male rat, *Drug Metab Disposition* **5**: 425-435 (1977).

39 Kotaki H, Nakazato F, Aoyama T, Saitoh Y, Nakagawa F, Interaction in tissue distribution between methylphenidate and pemoline. I. Tissue distribution of methylphenidate and its metabolite in the rat, Chem Pharm Bull **36**: 3190-3195 (1988).

40 Davila D, Kolacny-Babic L, Pharmacokinetics of azithromycin after single oral dosing of experimental animals, *Biopharm Drug Dispos* **12**: 505-514 (1991).

41 Lee HS, Lee MG, Stability, tissue metabolism, tissue distribution and blood partition of azosemide, *Biopharm Drug Dispos* **16**: 547-561 (1995).

42 Bonate PL, Swann A, Silverman PB, Preliminary physiologically based pharmacokinetic model for cocaine in the rat: model development and scale-up to humans, *J Pharm Sci*, **85**: 878-883 (1996).

43 Haddad S, Withey J, Lapare S, Law F, Krishnan K, Physiologically -based pharmacokinetic modeling of pyrene in the rat, *Environl Toxicol Pharmacol* **5**: 245-255 (1998).

44 Han, K. S., Kim, Y. G., Yoo, J. K., Lee, J. W. and Lee, M. G. Pharmacokinetics of a new reversible proton pump inhibitor, YH1885, after intravenous and oral administrations to rats and dogs: hepatic first-pass effect in rats, Biopharm Drug Dispos **19**: 493-500 (1998).

45 Yamamoto F, Oka H, Antoku S, Ichiya Y, Masuda K, Maeda M, Synthesis and characterisation of lipophilic 1-[F^{18}] fluoroalkyl-2-nitroimidazoles for imaging hypoxia. *Biol Pharm Bull* **22**: 590-597 (1999).

46 Aravagiri M, Teper Y, Marder SR, Pharmcokinetics and tissue distribution of olanzapine in

rats. *Biopharm Drug Dispo* **20**: 369-377 (1999).

47 Fazio F, Todde S, Moresco RM, Simonelli P, Baraldi PG, Cacciari B, Spalluto G, Varani K, Monopoli A, Matarrese M, Carpinelli A, Magni F, Kienle GK, Design, radiosynthesis, 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 (2000).

48 Nagaraja NV, Singh SK, Paliwal JK, Gupta RC, Tissue distribution and excretion of CDRI-81/470 in rats, *J Pharm Phamacol* **52**: 1257-1264 (2000).

49 Gasco MR., Fundaro A, Cavalli R, Bargoni A, Vighetto D, Non-stealth and stealth solid lipid nanoparticles (SLN) carrying doxorubicin: pharmacokinetics and tissue distribution after I.V. administration to rats, *Pharmacol Res* **42**: 337-343 (2000).

50 Corley RA, English JC, Hill TS, Fiorcia LA, Morgott D. A, Development of a physiologically based pharmacokinetic model for hydroquinone. *Toxicol Applied Pharmacol* **165**, 163-174 (2000).

51 Poulin P, Theil FP, 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 (2000).

52 Mclachlan AJ, Hosseini-Yegabeh M, Tissue distribution of terbinafine in rats, *J Pharm Sci* **90**: 1817-1828 (2001).

53 Bjorkman S, Prediction of the volume of distribution of a drug: which tissue-plasma partition coefficients are needed, *Pharm Pharmacol* **54**: 1237-1245 (2002).

54 Poulin P, Theil FP, Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition, *J Pharm Sci* **91**: 1358-1367 (2002).

55 Parham FM, Mathews HB, Portier CJA, Physiologically based pharmacokinetic model of p, p'-dichlorodiphenylsulfone, *Toxicol Applied Pharmacol* **181**: 153-163 (2002).

56 Wojcikowski J, Daniel WA, Thioridazine-fluoxetine interactions at the level of the distribution process in vivo, Pol J Pharmacol **54**, 647-654 (2002).

57 Doze P, Elsinga PH, Maas B, Van Waarde A, Wegman T, Vaalburg W, Synthesis and evaluation of radiolabelled antagonist for i-maging of β-adrenoceptors in the Brain with PET, *Neurochem Internat* **40**: 145-155 (2002).

58 Mclachlan AJ, Hosseini-Yegabeh M, Tissue distribution of terbinafine in rats, *J Pharm Sci* **90**: 1817-1828 (2001).

59 Ballard P, Leahy DE, Rowland M, Prediction of *in vivo* tissue distribution from *in vitro* data.3. Correlation between *in vitro* and *in vivo* tissue distribution of a homologous series of nine 5-n-alkyl-5-ethyl barbituric acids, Pharm Res **20**: 864-871 (2003).

60 Graham H, Walker M, Jones O, Yates J, Galetin A and Aarons L, Comparison of in-vivo and in-silico methods used for prediction of tissue : plasma partition coefficients in rats, J Pharm Pharmacol **64**: 383-396 (2011).

61 Mahle DA, Gearhart JM, Grigsby CC, Mattie DR, Barton HA, Lipscomb JC and Cook RS, Age-dependent partition coefficients for a mixture of volatile organic solvents in Sprague-Dawley rats and humans, *J Toxicol Env Health A* **70**: 1745-1751 (2007)

62 Crowell SR, Henderson WM, Kenneke JF and Fisher JW, Development and application of a physiologically based pharmacokinetic model for triadimefon and its metabolite triadeimenol in rats and humans. *Toxicol Letters* **205**: 154-162 (2011).

63 Schmitt W, General approach for the calculation of tissue to plasma partition coefficients, *Toxicol in Vitro* **22**: 457-467 (2008).

64 Peyret T, Poulin P and Krishnan K, A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals, Toxicol Applied Pharmacol **249**: 197-207 (2010)

65 Absolv, version 5.0, Advanced Chemistry Development, 110 Yonge Street, 14th Floor, Toronto, Ontario, M5C 1T4, Canada.

66 Stephens TW, Acree, Jr. WE, Twu P, Anderson JL, Baker GA and Abraham MH, Correlation of the solubilizing abilities of 1-butyl-1-methylpiperidinium bis(trifluoromethylsulfonyl)imide and 1-butyl-1-methylpyrrolidinium tetracyanoborate, *J Soln Chem* **41**: 165-1184 (2012)

Table 1. Saline-tissue partition coefficients, *in vitro*, as determined by Jepson *et al*.[8]

	Saline-tissue partition coefficients, as log P_{tiss} .[8]					
Compound	Blood	Fat	Muscle	Liver	Skin	Olive oil
Lindane	2.01	3.99	2.21	2.63	2.30	4.01
Parathion	1.74	3.74	2.15	2.46	2.23	n/a
Paraoxon	0.35	1.36	0.91	1.17	n/a	1.38
Trichloroacetic acid	0.41	-0.10	0.59 [a]	0.45 [a]	n/a	n/a
Dichloroacetic acid	0.08	-0.07	0.47 [a]	n/a	n/a	n/a
Tetrachloroethene	1.87	3.38	1.73	1.98	n/a	n/a

[a] Concentration dependent

Table 2. Saline-tissue and blood-tissue partition coefficients, *in vitro*, from Artola-Garicano *et al*. [9]

	Saline-tissue partition coefficients, as log P_{tiss}. [9]			
Compound	Blood	Fat	Muscle	Liver
Lindane	1.75	3.84	2.19	2.41
Parathion	1.73	3.53	2.15	2.34
Paraoxon	0.44	1.49	0.65	1.01
	Blood-tissue partition coefficients, as log P_{tiss} [a]			
Lindane		1.98/2.09	0.20/0.44	0.62/0.66
Parathion		2.00/1.80	0.41/0.42	0.72/0.61
Paraoxon		1.01/1.05	0.56/0.21	0.82/0.57

[a] Values given from ref 8 and ref 9.

Table 3. Blood-tissue partition coefficients, *in vitro*, from Tremblay *et al*. [10] Some values were not determined [10] and are denoted as n/d

	Blood-tissue partition coefficients, as log P_{tiss} [10]			
Compound	Liver	Brain	Kidney	Muscle
Pymetrozine	-0.35	-0.14	-0.14	n/a
Thiamethoxam	-0.17	-0.11	-0.01	-0.51
Mesotrione	-0.04	-0.18	-0.08	-0.44
Pirimicarb	-0.03	n/d	0.30	0.11
Thiabendazole	-0.05	-0.05	-0.13	0.00
Atrazine	-0.16	-0.15	n/d	n/d
Cyproconazole	0.58	0.28	0.18	-0.06
Ametryn	0.30	0.04	n/d	-0.04
Molinate	0.18	0.11	0.42	-0.31
Paclobutrazol	0.63	0.32	0.04	-0.11
Propiconazole I [a]	0.58	0.58	0.40	-0.04
Propiconazole II [a]	0.63	0.54	0.38	0.00
Cyprodinil	0.58	0.64	0.32	0.52

[a] These are two stereoisomers, ref 10.

Table 4. Partition coefficients *in vitro*, as log P_{tiss}, from saline to tissue for estradiol and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCPD).[12]

	Blood-tissue					Saline-phase	
Compound	Fat	Liver	Brain	Kidney	Muscle	Saline-fat	Saline-olive oil
Estradiol	-0.23	0.56	0.29			0.53	0.00
TCPD	2.27	0.66	0.84	0.52	0.65	2.97	3.96

1 **Table 5**. Coefficients in equations for *in viv*o partitions into rat tissue and *in vitro* partitions for

2 VOCs into human or rat tissue

System	S [a]	*c*	*e*	*s*	*a*	*b*	*v*	*l*	*Ic* [b]
Blood-brain/*in vivo* [16]	D	0.547	0.221	-0.604	-0.641	-0.681	0.635		-1.216
Blood-muscle/*in vivo* [17]	D	0.082	-0.059	0.010	-0.248	0.028	0.110		-1.022
Blood-liver/*in vivo* [19]	D	0.292	0.000	-0.296	-0.334	0.181	0.337		-0.597
Blood-lung/*in vivo* [20]	D	0.269	0.000	-0.523	-0.723	0.000	0.720		-0.988
Blood-kidney/ *in vivo* [c]	D	0.494	-0.067	-0.426	-0.367	0.232	0.410		-0.481
Blood-heart/ *in vivo* [c]	D	0.132	-0.039	-0.394	-0.376	0.009	0.527		-0.572
Blood-skin/*in vivo* [21]	D	-0.105	-0.117	0.034	0.000	-0.681	0.756		-0.816
Blood-fat/*in vivo* [18]	D	0.077	0.249	-0.215	-0.902	-1.523	1.234		-1.013
Skin permeation [23, d]	DV	-5.420	-0.102	-0.457	-0.324	-2.608	2.066		
Water-skin partition [22]	DV	0.523	0.101	-0.076	-0.022	-1.951	1.652		
Blood-brain/*in vitro* [14]	V	-0.057	0.017	-0.563	-0.323	-0.335	0.731		
Blood-muscle/*in vitro* [17]	V	-0.185	-0.209	-0.593	-0.081	-0.168	0.741		
Blood-liver/*in vitro* [19]	V	-0.095	0.000	-0.366	-0.357	-0.180	0.730		
Blood-lung/*in vitro* [20]	V	-0.143	0.000	0.000	0.000	-0.383	0.308		
Blood-kidney/*in vitro* [c]	V	-0.155	0.193	-0.462	-0.922	0.232	0.750		
Blood-heart/*in vitro* [c]	V	0.047	0.041	-0.045	0.083	-0.224	0.948		
Blood-fat/*in vitro* [18]	V	0.474	0.016	-0.005	-1.577	-2.246	1.560		
Saline-olive oil [24]	V	0.019	0.556	-0.980	-1.938	-4.640	4.223		
Gas-blood/*in vitro* [14]	V	-1.062	0.460	1.067	3.777	2.558		0.375	
Gas-brain/*in vitro* [14]	V	-0.987	0.263	0.411	3.358	2.025		0.591	
Gas-muscle/*in vitro* [17]	V	-1.039	0.207	0.723	3.242	2.469		0.463	
Gas-liver/*in vitro* [19]	V	-0.943	0.000	0.836	2.836	2.081		0.564	
Gas-lung/*in vitro* [20]	V	-1.250	0.639	1.038	3.661	3.043		0.420	
Gas-kidney/*in vitro* [c]	V	-1.005	0.489	0.774	3.000	2.719		0.497	
Gas-heart/ *in vitro* [c]	V	-1.199	0.185	0.596	2.951	2.450		0.589	

Gas-fat/*in vitro* [18]	V	-0.052	0.051	0.728	1.783	0.332		0.743	
Gas-olive oil [24]	V	-0.188	-0.095	0.851	1.468	0.000		0.873	
Gas-skin [21]	DV	-0.254	0.311	2.230	3.705	2.925		0.243	
Gas-water [25, e]	DV	-0.994	0.577	2.549	3.813	4.841	-0.869	0.000	
Gas-water [25, e]	DV	-1.271	0.822	2.743	3.904	4.814	0.000	-0.213	

[a] D drugs in rats; V VOCs in humans. [b] *Ic* is an indicator variable for carboxylic acids. [c] This work [d] The equation is for *in vitro* permeation, log *Kp* in cm s^{-1}, for a wide variety of compounds, see text.. [e] The gas-water partition coefficient, as log *Kw*, at 25°C.

Table 6. Observed and predicted *in vivo* blood-tissue partition coefficients, as log P_{tiss}

		Blood-tissue, log P_{tiss}			
Compound		Liver	Brain	Kidney	Fat
Triadimefon, *in vivo*	Obs	0.41	0.23	0.21	0.99
	Pred	0.71	0.35	0.79	0.87
	Pred [a]	0.62	0.59	0.77	0.90
Triadimenol, *in vivo*	Obs	0.84	0.18	0.44	0.46
	Pred	0.71	0.30	0.81	0.65
	Pred [a]	0.61	0.18	0.66	0.71

[a] Using Absolv calculated descriptors, see later.

1 **Table 7**. Descriptors for the compounds studied

Compound	*E*	*S*	*A*	*B*	*V*	*L*	log *Kw*
Lindane	1.45	0.91	0.00	0.68	1.5798	7.467	4.10
Parathion	1.44	0.93	0.00	1.04	1.9984	8.590	5.55
Paraoxon	1.11	1.72	0.00	1.20	1.8936	8.730	8.24
Pymetrozine	1.63	1.87	0.16	1.54	1.6001	8.550	11.40
Thiamethoxam	1.76	1.57	0.00	1.84	1.8076	9.092	11.38
Mesotrione	1.82	3.15	0.00	1.80	2.2372	12.140	14.90
Pirimicarb	1.18	1.33	0.00	1.34	1.8945	8.475	7.95
Thiabendazole	2.22	1.90	0.35	0.64	1.3967	8.762	8.35
Atrazine	1.22	1.29	0.17	1.01	1.6196	7.783	7.10
Cyproconazole	1.93	1.60	0.32	1.40	2.1618	10.730	10.37
Ametryn	1.47	1.23	0.19	1.02	1.8016	8.500	7.12
Molinate	0.88	1.09	0.00	0.70	1.5471	6.578	4.36
Paclobutrazol	1.53	1.39	0.21	1.46	2.2704	10.455	9.39
Propiconazole I	2.06	2.53	0.00	1.10	2.3429	12.300	10.00
Propiconazole II	2.06	2.53	0.00	1.10	2.3429	12.300	10.00
Cyprodinil	2.06	0.97	0.07	0.92	1.7968	9.097	5.84
Estradiol	1.80	1.77	0.86	1.10	2.1988	11.100	11.31
TCPD	2.05	1.69	0.00	0.00	1.8226	9.755	2.95
Triadimefon	1.68	1.79	0.00	1.24	2.1452	10.630	8.72
Triadimefon [a]	1.75	2.21	0.00	1.14	2.1452	10.080	

Triadimenol	1.60	1.58	0.26	1.28	2.1882	10.510	9.28
Triadimenol [a]	1.78	1.91	0.23	1.24	2.1882	10.200	

[a] Calculated descriptors from structure using Absolv, ref. 32.

Table 8. Predictions for blood-tissue distribution and for water-skin distribution as log *P*, and for permeation from water through skin as log Kp (cm s^{-1})

	Blood to tissue, log *P*									
Compound	Brain	Muscle	Liver	Lung	Kidney	Heart	Skin	Fat	Water-skin [a]	Skin perm
Lindane	0.86	0.20	0.68	0.93	0.81	0.56	0.49	1.16	1.88	-4.54
Parathion	0.86	0.26	0.88	1.22	1.06	0.77	0.56	1.12	1.87	-4.65
Paraoxon	0.14	0.28	0.64	0.73	0.74	0.42	0.44	0.49	1.29	-5.62
Pymetrozine	-0.36	0.18	0.50	0.33	0.54	0.13	-0.07	-0.43	0.18	-7.31
Thiamethoxam	-0.12	0.24	0.77	0.75	0.88	0.41	-0.14	-0.39	-0.02	-7.51
Mesotrione	-0.76	0.30	0.44	0.23	0.37	0.02	0.25	-0.13	0.65	-7.25
Pirimicarb	0.29	0.27	0.78	0.94	0.94	0.57	0.32	0.38	1.06	-5.83
Thiabendazole	0.12	0.05	0.20	0.03	0.13	-0.09	0.32	0.65	1.65	-5.46
Atrazine	0.27	0.19	0.58	0.64	0.70	0.37	0.33	0.41	1.25	-5.55
Cyproconazole	0.22	0.18	0.69	0.76	0.78	0.46	0.4	0.46	1.43	-5.74
Ametryn	0.46	0.19	0.66	0.79	0.78	0.48	0.43	0.68	1.56	-5.21
Molinate	0.59	0.23	0.62	0.81	0.77	0.49	0.52	0.9	1.72	-4.69
Paclobutrazol	0.36	0.24	0.84	1.02	0.99	0.66	0.48	0.55	1.47	-5.5
Propiconazole I	0.21	0.27	0.53	0.63	0.49	0.30	0.76	1.26	2.26	-4.89
Propiconazole II	0.21	0.27	0.53	0.63	0.49	0.30	0.76	1.26	2.26	-4.89
Cyprodinil	0.89	0.18	0.75	1.00	0.87	0.60	0.42	1.13	1.83	-4.85
Estradiol	-0.03	0.05	0.42	0.30	0.46	0.21	0.66	0.41	2.04	-5.10

TCPD	1.14	0.18	0.41	0.70	0.38	0.35	1.09	2.47	3.61	-2.64
Triadimefon	0.35	0.27	0.71	0.88	0.79	0.50	0.54	0.87	1.68	-5.30
Triadimefon [b]	0.59	0.23	0.62	0.81	0.77	0.49	0.52	0.90	1.72	-4.69
Triadimenol	0.30	0.21	0.71	0.83	0.81	0.51	0.54	0.65	1.68	-5.30
Triadimenol [b]	0.18	0.21	0.61	0.68	0.66	0.39	0.56	0.71	1.75	-5.35

1 [a] Eqn. (11). [b] Using the Absolv calculated descriptors in Table 7.