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

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11 **Running title:** The prediction of blood-tissue partitions, water-skin partitions and skin
12 permeation

13 **Abstract**

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

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

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

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

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

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13

14 **1 INTRODUCTION**

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

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

$$3 \quad K_s = \text{conc of compound in condensed phase (mol dm}^{-3}\text{)} / \text{conc. of compound in the gas phase} \\ 4 \quad (\text{mol dm}^{-3}) \quad (1)$$

5 The GLC headspace method has been used regularly³⁻⁶ to obtain *in vitro* gas-blood and gas-
6 tissue partition coefficients for volatile organic compounds, VOCs. These are defined as organic
7 compounds with boiling points below around 260°C. Since it is rather impractical to determine
8 the concentration of a compound in a biological tissue by GLC, a procedure particularly
9 developed by Gargas et al.⁵ has been used. A fixed amount of the compound is added to an
10 empty vial and a vial containing the tissue. The headspace concentrations are determined by
11 GLC and the concentration in the tissue obtained by difference. Meulenberg and Vijverberg⁷
12 list numerous gas-tissue partition coefficients that have been determined in this way. Once K_s has
13 been found for blood (K_{blo}) and a tissue (K_{tis}) for a given compound, then the corresponding
14 blood-tissue partition coefficient, P_{tis} can be obtained from eq (2); C_{tis} and C_{blo} are the
15 equilibrium concentrations in tissue and blood.

$$16 \quad P_{tis} = K_{tis} / K_{blo} = C_{tis} / C_{blo} \quad (2)$$

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

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

3 Table 1 here

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

11 Table 2 here

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

18 Table 3 here

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

1 tetrachloro-p-dioxin, TCPD, are in Table 4. The method developed by Jepson *et al.*⁸ is quite
2 general and is not limited to VOCs. Indeed, the compounds studied by Tremblay *et al.*¹⁰
3 included nonvolatile herbicides, insecticides and fungicides. It is very important to note that the
4 procedure developed by Gargas *et al.*,⁵ by Jepson *et al.*⁸ and by Tremblay *et al.*¹⁰ yields values
5 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*
6 *vivo* values

7 Table 4 here

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

20

21

1 2 METHODS

2 Our method makes use of the two linear free energy relationships, LFERS,^{26, 27} eqns. (3) and
3 (4).

$$4 \quad \text{Log } P = c + eE + sS + aA + bB + vV \quad (3)$$

$$5 \quad \text{Log } K = c + eE + sS + aA + bB + lL \quad (4)$$

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

9 The independent variables in eqns. (3) and (4) are the Abraham solute descriptors as follows.

10 ^{26, 27} E is the solute excess molar refractivity in units of $(\text{cm}^3 \text{ mol}^{-1})/10$, S is the solute dipolarity
11 / polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, and V
12 is the McGowan characteristic volume in units of $(\text{cm}^3 \text{ mol}^{-1})/100$. L is the gas-hexadecane
13 partition coefficient at 298 K. The solute descriptors are obtained from a variety of experimental
14 data, including water-solvent partition coefficients, solubilities in organic solvents, and
15 chromatographic data, as detailed by us previously.^{27, 28} Clarke and Mallon²⁹ have given a
16 detailed description our entire method, including the determination of the Abraham solute
17 descriptors. The coefficients in eqns. (3) and (4) are obtained by multiple linear regression
18 analysis, and serve to characterize the system under consideration. These coefficients are listed
19 in Table 5 for *in vitro* partition from gas to tissue and from blood (plasma) to tissue for volatile
20 organic compounds in rats and humans, for *in vivo* partition from blood to tissue in rats for
21 drugs, and for *in vitro* partition from water to skin in humans for drugs. In addition we include an
22 important equation for *in vitro* permeation of compounds from water through human skin. We
23

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

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

17 Table 5 here

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

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

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

$$6 \quad N = 70, SD = 0.252, R^2 = 0.955, F = 273.5$$

7

$$8 \quad \text{Log } P_{\text{kidney}}(\text{VOCs}) = -0.155 + 0.193 E - 0.462 S - 0.922 A + 0.232 B + 0.750 V \quad (6)$$

$$9 \quad N = 70, SD = 0.218, R^2 = 0.593, F = 18.6$$

10

$$11 \quad \text{Log } P_{\text{kidney}}(\text{Drugs}) = 0.494 - 0.067 E - 0.426 S - 0.367 A + 0.232 B + 0.410 V - 0.481 I_c$$

$$12 \quad N = 110, SD = 0.460, R^2 = 0.474, F = 15.5, PSD = 0.488 \quad (7)$$

13

$$14 \quad \text{Log } P_{\text{kidney}}(\text{Drugs}) = 0.485 - 0.071 E - 0.391 S - 0.309 A + 0.186 B + 0.414 V - 0.513 I_c$$

$$15 \quad N = 124, SD = 0.448, R^2 = 0.462, F = 16.9, PSD = 0.474$$

$$16 \quad \text{PRESS} = 26.53, Q^2 = 0.399,$$

17

18

19

$$20 \quad \text{Log } K_{\text{heart}}(\text{VOCs}) = -1.199 + 0.185 E + 0.596 S + 2.951 A + 2.450 B + 0.589 L \quad (8)$$

1 $N = 31, SD = 0.159, R^2 = 0.981, F = 264.3$

2

3 $\text{Log } P_{heart}(\text{VOCs}) = -0.458 + 0.041 E - 0.045 S - 0.881 A - 0.224 B + 0.948 V$ (9)

4 $N = 31, SD = 0.194, R^2 = 0.719, F = 12.8$

5

6 $\text{Log } P_{heart}(\text{Drugs}) = 0.132 - 0.039 E - 0.394 S - 0.376 A + 0.009 B + 0.527 V - 0.572 Ic$

7 $N = 89, SD = 0.453, R^2 = 0.512, F = 14.3, \text{PSD} = 0.556$ (10)

8 $\text{Log } P_{heart}(\text{Drugs}) = 0.194 - 0.067 E - 0.313 S - 0.334 A + 0.025 BS + 0.449 V - 0.526 Ic$

9 $N = 107, SD = 0.404, R^2 = 0.496, F = 16.4, \text{PSD} = 0.479$

10 $\text{PRESS} = 22.9626 \quad \text{R-Sq(pred)} = 29.15\%$

11

12

13

14

15

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

1 Abraham and Martins²² set out an equation for the partition of 45 varied solutes between
 2 water and human *stratum corneum*, *SC*. We have updated the equation using more recent
 3 descriptors based on additional experimental data, as eqn. (11), and include the coefficients in
 4 Table 5. We can also combine the $\log P_{SC}$ values with $\log K_w$ values for partition from the gas
 5 phase to water to obtain $\log K_{SC}$ values for partition from the gas phase to (water saturated) *SC*.
 6 The corresponding equation is given as eqn. (12).

$$7 \quad \text{Log } P_{SC} (\text{Drugs/VOCs}) = 0.523 + 0.101 E - 0.076 S - 0.022 A - 1.951 B + 1.652 V$$

$$8 \quad N = 45, SD = 0.221, R^2 = 0.909, F = 77.7 \quad (11)$$

$$9 \quad \text{Log } K_{SC} (\text{Drugs/VOCs}) = -0.254 + 0.311 E + 2.230 S + 3.705 A + 2.925 B + 0.243 L$$

$$10 \quad N = 45, SD = 0.201, R^2 = 0.999, F = 11842.9 \quad (12)$$

11

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

$$19 \quad \text{Log } K_p = -5.420 - 0.102 E - 0.457 S - 0.324 A - 2.680 B + 2.066 V - 1.938 J^+ + 2.548 J^- \quad (13)$$

1

2 **3 RESULTS**

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

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

20

Table 6 here

1 For the eight sets of observed and predicted $\log P_{tiss}$ values in Table 6, $AE = -0.14$, $AAE =$
2 0.20 , $RMSE = 0.26$ and $SD = 0.27$ log units. Given that there will be an associated error in the
3 observed $\log P_{tiss}$ values, the small AE of -0.14 log units, and the total SD error of 0.27 log units,
4 suggests that the *in vivo* equations in Table 5 do yield reasonable predictions of *in vivo* blood-
5 tissue partitions.

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

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

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

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

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

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

5 Table 7 here

6 Table 8 here

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

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

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

5

6 **4 CONCLUSION**

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

12 In addition to the predictions already given in Table 8, once the descriptors in eqn. (1) and
13 eqn. (2) have been obtained for a given agrochemical, it is also possible to predict values for
14 numerous other processes. These include partition coefficients from water and the gas phase to a
15 very large number of organic solvents²⁸ and from water and the gas phase to room temperature
16 ionic liquids.⁶⁶ Clarke and Mallon²⁹ have listed Abraham descriptors for a number of
17 agrochemicals; these descriptors can be combined with the equation coefficients given in Table 5
18 to obtain values for the various processes by simple arithmetic.

19

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

Compound	Saline-tissue partition coefficients, as $\log P_{tiss}$. ⁸					
	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

4 ^a Concentration dependent

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3 **Table 2.** Saline-tissue and blood-tissue partition coefficients, *in vitro*,4 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

5 ^a Values given from ref 8 and ref 9.

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Table 3. Blood-tissue partition coefficients, *in vitro*, from Tremblay *et al.*¹⁰ Some values were not determined¹⁰ and are denoted as n/d

Compound	Blood-tissue partition coefficients, as $\log P_{tiss}$ ¹⁰			
	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.

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4 **Table 4.** Partition coefficients *in vitro*, as $\log P_{tiss}$, from saline to tissue for estradiol and 2,3,7,8-5 tetrachlorodibenzo-p-dioxin (TCPD).¹²

Compound	Blood-tissue					Saline-phase	
	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

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- 1 **Table 5.** Coefficients in equations for *in vivo* 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/ <i>in vivo</i> ¹⁶	D	0.547	0.221	-0.604	-0.641	-0.681	0.635		-1.216
Blood-muscle/ <i>in vivo</i> ¹⁷	D	0.082	-0.059	0.010	-0.248	0.028	0.110		-1.022
Blood-liver/ <i>in vivo</i> ¹⁹	D	0.292	0.000	-0.296	-0.334	0.181	0.337		-0.597
Blood-lung/ <i>in vivo</i> ²⁰	D	0.269	0.000	-0.523	-0.723	0.000	0.720		-0.988
Blood-kidney/ <i>in vivo</i> ^c	D	0.494	-0.067	-0.426	-0.367	0.232	0.410		-0.481
Blood-heart/ <i>in vivo</i> ^c	D	0.132	-0.039	-0.394	-0.376	0.009	0.527		-0.572
Blood-skin/ <i>in vivo</i> ²¹	D	-0.105	-0.117	0.034	0.000	-0.681	0.756		-0.816
Blood-fat/ <i>in vivo</i> 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/ <i>in vitro</i> ¹⁴	V	-0.057	0.017	-0.563	-0.323	-0.335	0.731		
Blood-muscle/ <i>in vitro</i> ¹⁷	V	-0.185	-0.209	-0.593	-0.081	-0.168	0.741		
Blood-liver/ <i>in vitro</i> ¹⁹	V	-0.095	0.000	-0.366	-0.357	-0.180	0.730		
Blood-lung/ <i>in vitro</i> ²⁰	V	-0.143	0.000	0.000	0.000	-0.383	0.308		
Blood-kidney/ <i>in vitro</i> ^c	V	-0.155	0.193	-0.462	-0.922	0.232	0.750		
Blood-heart/ <i>in vitro</i> ^c	V	0.047	0.041	-0.045	0.083	-0.224	0.948		
Blood-fat/ <i>in vitro</i> 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/ <i>in vitro</i> ¹⁴	V	-1.062	0.460	1.067	3.777	2.558		0.375	
Gas-brain/ <i>in vitro</i> ¹⁴	V	-0.987	0.263	0.411	3.358	2.025		0.591	
Gas-muscle/ <i>in vitro</i> ¹⁷	V	-1.039	0.207	0.723	3.242	2.469		0.463	
Gas-liver/ <i>in vitro</i> ¹⁹	V	-0.943	0.000	0.836	2.836	2.081		0.564	
Gas-lung/ <i>in vitro</i> ²⁰	V	-1.250	0.639	1.038	3.661	3.043		0.420	
Gas-kidney/ <i>in vitro</i> ^c	V	-1.005	0.489	0.774	3.000	2.719		0.497	
Gas-heart/ <i>in vitro</i> ^c	V	-1.199	0.185	0.596	2.951	2.450		0.589	

Gas-fat/ <i>in vitro</i> 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	

1 ^a D drugs in rats; V VOCs in humans. ^b *Ic* is an indicator variable for carboxylic acids. ^c This

2 work ^d The equation is for *in vitro* permeation, $\log Kp$ in cm s^{-1} , for a wide variety of

3 compounds, see text.. ^e The gas-water partition coefficient, as $\log Kw$, at 25°C.

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

Compound		Blood-tissue, $\log P_{tiss}$			
		Liver	Brain	Kidney	Fat
Triadimefon, <i>in vivo</i>	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, <i>in vivo</i>	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

4 ^a Using Absolv calculated descriptors, see later.

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

Compound	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	<i>L</i>	log <i>K_w</i>
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	

1 ^a Calculated descriptors from structure using Absolv, ref. 32.

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

Compound	Blood to tissue, $\log P$								Water-skin ^a	Skin perm
	Brain	Muscle	Liver	Lung	Kidney	Heart	Skin	Fat		
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.