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Draize Rabbit Eye Test Compatibility with Eye Irritation Thresholds in Humans: A Quantitative Structure-Activity Relationship Analysis

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Short title: Draize Rabbit Eye Test and Effects in Humans

ABSTRACT

Draize rabbit eye test scores, as modified maximum average score, MMAS, for 68 pure bulk liquids were adjusted by the liquid saturated vapor pressure P^o. These 68 adjusted scores, as log (MMAS/ P^o), were shown to be completely equivalent to eye irritation thresholds, EIT expressed as log (1/EIT), for 23 compounds in humans. Thus for the first time the Draize eye test in rabbits for pure bulk liquids is shown to be perfectly compatible with eye irritation thresholds in humans. The total data set for 91 compounds was analyzed by the general solvation equation of Abraham. Values of log (MMAS/ P^o) or log (1/EIT) could be fitted to a five-parameter equation with $R^2 = 0.936$, SD = 0.433, AD =0.000, and AAD = 0.340 over a range of 9.6 log units. When divided into a training set of 45 compounds, the corresponding equation could be used to predict the remaining 46 compounds in a test set with AD = -0.037 and AAD = 0.345 log units. Thus the 91 compound equation can now be used to predict further EIT values to around 0.4 log units.

It is suggested that the mechanism of action in the Draize test and in the human eye irritation thresholds involves passive transfer of the compound to a biophase that is quite polar, is a strong hydrogen bond base, a moderate hydrogen bond acid and quite hydrophobic. The biophase does not resemble water or plasma, but resembles an organic solvent such as N-methylformamide.

INTRODUCTION

The Draize rabbit eye test (Draize *et al*., 1944) is the only widely used assay for the effect of substances on the eye. In view of the scientific, ethical and economic concerns over the Draize test (Wilhelmus, 2001) it is not surprising that alternatives to the Draize test have been examined, and that various calculation procedures have been published. An in depth study (Brantom *et al*., 1997) of a number of alternative assays has been carried out, but the conclusion was that none of them could be regarded as a valid replacement for the Draize test. On the other hand, it has been suggested (Spielmann *et al*., 1998) that a combination of two *in vitro* tests could be used to identify severe irritants. One challenge in finding alternatives to the Draize test is that the available data covers compounds in a variety of physical forms – liquids, solids, and aqueous solutions. The actual mechanism of irritation may well not be the same over all these forms, and this would preclude any general alternative test or any general calculation.

Fragmentation schemes for particular chemical or biological effects attempt to relate the effect to structural fragments of molecules. These may be functional groups, or just parts of molecules such as the CH_3 or CH_2 fragment. Then an effect is assigned to each fragment, and predictions are made by summation of the fragment effects in a given molecule. Such schemes for the estimation of eye irritation have been reported (Enslein, 1988; Klopman *et al*., 1993) but most of the data used by Enslein were not Draize scores. Although Klopman *et al.* (1993) used Draize scores, these were used in conjunction with other judgements; unfortunately, the full list of compounds studied is not available. Other workers have restricted their analyses to pure organic compounds. Principal components analysis, PCA, and neural networks (Chamberlain and Barratt, 1995; Barratt, 1995, 1997) have been used to discriminate between irritants and non-irritants with reasonable success. On the other hand, investigation of a similar data set using linear combinations of descriptors and PCA (Cronin

et al., 1994) failed to generate any general linear correlation of modified Draize scores and failed to observe any marked distinction between irritants and non-irritants by PCA. The modified Draize scores were defined as MMAS divided by the molarity of the pure liquid; the latter is given by 1000 times the density of the pure liquid divided by the liquid molecular weight. The descriptors of the compounds in the best linear equation were ClogP where P is a calculated water-octanol partition coefficient, LUMO the lowest unoccupied molecular orbital, and a connectivity index. Cronin *et al*. (1994) correctly pointed out that use of a physically heterogeneous set of compounds, that is pure liquids, solids and aqueous solutions, would make it very difficult to obtain any useful structure-activity relationship, SAR, and so restricted their analysis to pure bulk liquids. Kulkarni and Hopfinger (1999) obtained a reasonable relationship, but only for a very limited set of 18 compounds in a training set and five in a test set. Patlewicz *et al.* (2000) restricted their analysis to cationic surfactants, and for this set of compounds found a very good fit of observed and calculated Draize eye scores using a neural network.

What is surprising is that the above efforts have been expended before any substantial connection between results of the Draize test in rabbits and the effect of the corresponding substances in man has been established. In a comprehensive review of the Draize test, it was noted that the anatomy and biochemistry of the rabbit eye are not the same as those of the human eye, and that there were a number of physiological reasons such as low tear production, blink frequency and ocular surface area why such a test on rabbits might not adequately predict human effects (Wilhelmus, 2001). York and Steiling (1998) stressed the need to validate the Draize test against controlled human eye data, but noted that "there are no adequate human data." What comparisons have been made between effects on rabbits and effects on humans have been confined to consumer products that are a mixture of various chemicals. Freeberg *et al*. (1986) examined four such products and showed that the low-

volume Draize test correlated with effects on the eyes of humans better than did the normal volume Draize test. Allgood (1989) also matched the low-volume Draize test against human experience for four shampoos, and Griffith (1989) compared Draize data to consumer eye accident data for soaps and detergents. Roggeband *et al*. (2000) studied the effect of very low volumes (1-3 μl) of a liquid detergent and a dishwashing liquid on the eyes of rabbits and human volunteers. They observed that the irritation responses in rabbits were greater than those in man, and suggested that the low-volume Draize test could be used to assess eye irritation hazards in man.

One problem until recently has been the lack of controlled human eye data (York and Steiling, 1998) but this has been rectified by the determination of eye irritation thresholds, EIT, in humans by a rigorous standardized procedure (Cometto-Muñiz and Cain, 1991, 1995, 1998; Cometto-Muñiz *et al.,* 1997, 1998 a, 1998 b). It is these EIT values that we shall use.

For the substances studied in the Draize test as pure bulk liquids, no adequate connection between effects on rabbits and effects on humans has been established, although for a limited number of liquids an indirect connection has been indicated (Abraham *et al*. 1998a,b). It is the purpose of this work to use the indirect method on a large data set to establish whether or not such a connection exists, and, if successful to use the connection to obtain a quantitative structure-activity relationship (QSAR) for eye irritation thresholds in man. The Draize test scores, MMAS, that we use are those for pure bulk liquids as recorded in the ECETOC manual (ECETOC, 1998). We used values for all the pure bulk liquids given, except for a number of high boiling liquids for which vapor pressures at 298 K were either unknown or were unreliable.

METHODS

Comparison of Draize scores and eye irritation thresholds

The Draize test scores, MMAS, that we shall use (ECETOC, 1998) refer to the effect of pure bulk liquids, whereas the eye irritation thresholds, EIT in ppm, are established from the effect of the vapor of liquids at some particular partial pressure. Hence a direct comparison of MMAS and EIT is not possible. Consider the transfer of a compound from the vapor phase to a solvent phase, the equilibrium constant being defined as,

$$K = [\text{conc of compound in solvent}]/[\text{conc of compound in vapor phase}] \quad (1)$$

The compound can also be transferred from the bulk liquid to the solvent phase, the equilibrium constant being just the solubility of the bulk liquid,

$$S = [\text{conc of compound in solvent}] \quad (2)$$

These two equilibrium constants are related through the saturated vapor pressure, P^o, of the pure bulk liquid,

$$S = P^o * K \quad \text{or} \quad \log (S/ P^o) = \log K \quad (3)$$

This is illustrated in Fig. 1(a). Exactly the same relationship can be shown for the transfer to a biophase, such as a rabbit or human eye, rather than to a solvent, see Fig. 1(b). The transfer from the bulk liquid to the biophase is proportional to the Draize eye score, MMAS, provided that the mechanism of the Draize test involves passive transport to the site of action. Then

with this assumption, following Eq. (3) and Fig. 1, the Draize scores can be converted to scores for the effect of vapors through Eq. (4), where m is some constant.

$$\text{Log } (\text{MMAS}/ P^o) = \log K + m \quad (4)$$

If, again, we assume passive transfer of vapors to the biophase in human eye irritation, then log (EIT) will be given by the same type of equation,

$$\text{Log } (1/\text{EIT}) = \log K' + m' \quad (5)$$

We prefer to use log (1/EIT) because the greater the value, the more potent is the compound. Then combination of Eq. (4) and Eq. (5) leads to Eq. (6), which can be used as a starting point for any comparison of MMAS values with EIT values. Since EIT values are listed in ppm, we use P^o in ppm, and at 298 K in Eq. (6).

$$\text{Log } (\text{MMAS}/ P^o) = \log (1/\text{EIT}) + m'' \quad (6)$$

QSAR studies

Our procedure is to use log (MMAS/ P^o) or log (1/EIT) as the dependent variable, SP, and to construct QSARs through Eq. (7), the general equation that we have developed (Abraham, 1993; Abraham and Al-Hussaini, 2002a). In Eq. (7) the independent variables are compound descriptors as follows. **E** is the solute excess molar refractivity, in units of $(dm^3 mol^{-1})/10$, **S** is the solute dipolarity/polarizability, **A** and **B** are the overall or summation hydrogen bond acidity and basicity, and **L** is the logarithm of the gas-hexadecane partition

coefficient. Our rationale in using the particular descriptors in Eq. (7) was that we had already used this equation to fit and interpret a number of gas-to-solvent partitions. Since we suggest that (MMAS/ P^o) or (1/EIT) are related to gas-to-biophase partition, see Fig. 1, it is logical to use Eq. (7), at least as a first step, in the analysis of log (MMAS/ P^o) or log (1/EIT). In order to investigate whether QSARs based on Eq. (7) might be improved by inclusion of other types of descriptors, we calculated shape descriptors using the HyperChem software (HyperChem, 2000), with conformational energy minimized using the AM1 semi-empirical method. **VG** is the three dimensional volume of the minimum energy conformation computed using the HyperChem QSAR option. **LG** is the longest length of the minimum energy conformation. In addition we investigate a shape descriptor, **DPO1**, calculated from the Dragon software (Todeschini *et al*., 2002) after conformational energy minimization by HyperChem. **DPO1** is a molecular descriptor derived from the distance distribution moments of the geometry matrix defined as the average row sum of its entries. It can be regarded as a shape descriptor that takes account of branching and of the distance of atoms from a center of gravity of a molecule

$$SP = c + e.\mathbf{E} + s.\mathbf{S} + a.\mathbf{A} + b.\mathbf{B} + l.\mathbf{L} \qquad (7)$$

The coefficients in Eq. (7) and other equations are evaluated through multiple linear regression analysis. The statistics that we shall detail are N the number of data points, R^2 the coefficient of variation, SD the standard deviation, AD the average deviation, AAD the absolute average deviation and F the Fischer statistic.

RESULTS AND DISCUSSION

Comparison of MMAS and EIT values

The most satisfactory comparison of log (MMAS/ P^o) and log (1/EIT) would be a direct comparison using Eq. 6. Unfortunately, log (MMAS/ P^o) and log (1/EIT) values are only available for nine common compounds in Table 1. For these nine compounds, log (MMAS/ P^o) = log (1/EIT) + 0.89 with AAD = 0.57, but this is not sufficient at all to demonstrate that MMAS is related to EIT. A much better method, that uses the information on log (MMAS/ P^o) and log (1/EIT) for all the compounds in Table 1, is to combine the two sets of data and to determine whether or not the same QSAR will fit the two sets. A straightforward method is to include a new descriptor, **I**, in Eq. (7) that takes the value **I** = 0 for the log (1/EIT) series of compounds and **I** = 1 for the log (MMAS/P^o) series of compounds. This **I**-descriptor takes into account data on all 91 compounds and, within the statistics of Eq. (8), below, shows that for any compound there is a constant difference between log (MMAS/P^o) and log (1/EIT). On Eq. (8) this difference is 0.568 ± 0.106 log units, which is in agreement with the difference of 0.89 ± 0.57 found for nine compounds only. For a total of 91 compounds we constructed Eq. (8) where SP = log (MMAS/ P^o) or log (1/EIT). There was only one outlier that we omitted, namely dodecane.

$$SP = -7.892 - 0.379\mathbf{E} + 1.872\,\mathbf{S} + 3.776\,\mathbf{A} + 1.169\,\mathbf{B} + 0.785\,\mathbf{L} + 0.568\,\mathbf{I} \qquad (8)$$

$N = 91$, $R^2 = 0.936$, SD = 0.433, AD =0.000, AAD = 0.340, F = 204.5

The 23 points for log (1/EIT) all fall on the line of identity, as shown in Fig. 2. If the deviations from the line for these 23 points are calculated separately, then AAD = 0.371 and AD = 0.000, the latter showing that there is no bias whatsoever in the fitting of the 23 log (1/EIT) points to Eq. (8). We can conclude that for the 68 values of log (MMAS/ P^o) and the

23 values of log (1/EIT) the two sets of data are compatible. Since the two sets both cover a range of variation of compound type, we suggest that this finding is quite general. The combined equation, Eq.(8), includes data on aliphatic and aromatic hydrocarbons and halogenated hydrocarbons, alcohols, ketones, acids, esters, nitro compounds, sulfides and terpenes, as well as pyridine and 4-fluoroaniline. We therefore feel that this equation is of such generality that it can be used to predict eye irritation thresholds in man for a host of chemical vapours.

Inspection of Fig. 2 shows that the range of log (MMAS/ P^o) is much wider than that of log (1/EIT) with a number of compounds having very positive values of log (MMAS/ P^o). These are all very involatile liquids, with vapor pressures so low that they will elicit no response in human subjects. This illustrates one advantage of including the log (MMAS/ P^o) data; compounds can be assigned log (1/EIT) values by this indirect method, even though log (1/EIT) cannot be determined directly. Another advantage is that compounds can be included that cannot be studied on humans for ethical reasons. Thus benzene and the sulfides can be assigned indirect log (1/EIT) values in this way.

If the two data sets are, indeed compatible, then similar equations to Eq. (8) should be obtained if the two sets are treated separately (although the coefficient of **I** must then be zero). There is not enough data on log (1/EIT) to obtain an equation with five variables, but for the log (MMAS/ P^o) set we find,

$$\text{Log (MMAS/ } P^o) = -7.355 - 0.351\mathbf{E} + 1.997\mathbf{S} + 4.380\,\mathbf{A} + 1.159\,\mathbf{B} + 0.758\,\mathbf{L} \quad (9)$$

$N = 68$, $R^2 = 0.954$, SD = 0.398, AD = 0.000, AAD = 0.318, F = 255.8

Eq. (9) is statistically the same as Eq. (8): note that the SD on the coefficients in these equations averages at around 0.30 except for the l-coefficient where it is 0.03, much smaller.

Thus on the basis that Eq. (8) and Eq. (9) are statistically the same, and that the data on log (1/EIT) exactly fit the general Eq. (8), we conclude that the Draize eye scores, modified by the compound vapor pressure, can be combined with the eye irritation thresholds into one equation. Except for our preliminary report on considerably fewer compounds (Abraham *et al*., 1998b) this is the first time that any real connection between Draize eye scores and effects on humans has been established for the important group of pure bulk liquids.

There is enough data in the two combined sets to test the predictive power of Eq. (8). We ranked the data in order of SP and chose every other compound as a training set. For the 45 compounds we found,

$$SP = -7.856 - 0.034\,\mathbf{E} + 1.529\,\mathbf{S} + 3.656\,\mathbf{A} + 1.555\,\mathbf{B} + 0.686\,\mathbf{L} \qquad (10)$$

$N = 45$, $R^2 = 0.921$, SD =0.469, AD =0.000, AAD =0.354, F = 74.0

The statistics of Eq. (10) are comparable to those of the full Eq. (8), bearing in mind the SD-values of the various coefficients, as noted above. Then we can use Eq. (10) to predict the remaining 46 compounds in the test set, that have not been used to derive Eq. (10). Results are in Table 2. Eq. (10), and hence the full Eq. (8), can predict SP values, where SP = log (MMAS/ P^o) and log (1/EIT) with almost no bias, since AD = -0.04, AAD = 0.35 and SD = 0.43 log unit. Considering that the 90 values cover a range of 9.7 log units and that the 23 log (1/EIT) values cover a range of 4.0 log units, we suggest that the full Eq. (8) can be used to predict log (1/EIT) values to within 0.45 log units, quite generally.

Interpretation of the QSAR results

The QSAR, Eq. (8), has been constructed on the assumption that the Draize eye scores and the human eye irritation thresholds result from passive transfer from the bulk liquid and the vapor phase respectively, to a biophase. Such passive transfer is usually non-specific, in that the position of a substituent has little effect, unless there is some particular interaction between the substituents. We can illustrate this through examination of water-octanol partition coefficients, as log Poct (Leo, 2002), see Table 3. The position of substituents has almost no effect except for o-hydroxybenzamide where the substituents interact. The statistics of Eq. (8) show that 94% of the information on log (MMAS/ P^o) and log (1/EIT) can be accounted for on the basis of passive transfer. There remains the possibility that the remaining 6% information applies to transfer from the biophase to some receptor. We would expect such transfer to be more specific; in particular the shape of a compound might be crucial. To examine this point, we include the three 'shape' descriptors in a QSAR and find,

$$SP = -6.944 - 1.201\,\mathbf{E} + 1.187\,\mathbf{S} + 3.268\,\mathbf{A} + 1.445\,\mathbf{B} + 1.445\,\mathbf{L} + 0.554\,\mathbf{I}$$
$$+0.084\,\mathbf{DPO1} - 0.007\,\mathbf{VG} + 0.031\,\mathbf{LG} \qquad (11)$$

$N = 91$, $R^2 = 0.941$, SD = 0.422, AD =0.000, AAD =0.334, F = 144.0

The additional shape descriptors have almost no effect, and so we consider that the main mechanistic step in human eye irritation and in rabbit eye irritation, is a simple passive transfer of a compound as a bulk liquid or as a vapor to a biophase. This partly explains the comment (Cronin *et al*., 1994) that construction of a QSAR for a physically heterogeneous set of compounds is very difficult. For compounds that are tested on rabbits as solids or as aqueous solutions, the passive transfer mechanism shown in Fig. 1will not hold. It has been noted (York and Steiling, 1998) that solids can cause irritancy through abrasive, mechanical

effects, and that Draize scores on solutions of liquids cannot be used to assess the irritancy of the pure bulk liquids. Nevertheless, molecular size can be crucial in a fundamental aspect: Although Table1 includes some quite large compounds such as iso-propyl iso-stearate, studies of eye and nose irritation from members of homologous series have indicated the existence of a cut-off effect in homologous series beyond which larger homologs fail to evoke irritation (cf. Cometto-Muñiz *et al*., 1998c). If, as suggested (Cometto-Muñiz *et al*., 1998c), such cut-off rests on a biological restriction (i.e., a receptor-related effect) rather than a physical restriction (i.e., just a low vapor pressure effect), then modeling the dimensional commonalities among cut-off molecules will serve to define the maximum molecular dimensions that the receptor can fit. We are, at present, exploring this issue.

Some information about the nature of the biophase can be obtained by a comparison of the coefficients in Eq. (8) with those for passive transfer from the vapor to various phases that might be considered models for the biophase. In Table 4 are collected the coefficients in Eq. (8) for transfer from the vapor to water (Abraham *et al*., 1994), and a number of organic solvents (Abraham *et al*., 2000, 2001). These coefficients are also known for transfer from the vapor to a number of biological tissues (Abraham and Weathersby 1994) and from the vapor to a plant cuticular polymeric membrane matrix (Platts and Abraham 2000).

Inspection of the data in Table 4 shows that the biophase cannot resemble either water or a largely aqueous phase such as plasma. The aqueous phases have very small *l*-coefficients (-0.213 and 0.157) whereas the biophase is relatively hydrophobic with $l = 0.787$, quite close to that for many organic solvents. By comparison to organic solvents, the biophase is dipolar with $s = 2.02$, almost the same as that for N-methylformamide. The biophase is a strong hydrogen bond base with $a = 4.02$, nearly as strong as the amides. It is also a moderately strong hydrogen bond acid, with $b = 1.15$, compare 1.43 for wet 1-octanol. The nearest organic solvent as regards these chemical properties is the secondary amide, N-

methylformamide. Interestingly, the plant polymeric membrane matrix has also quite similar properties to the biophase, but is rather less polar, less acidic and less basic. The biophase cannot be situated near to an aqueous mucus layer, and is more likely to be composed of amides (peptides) in a poorly aqueous environment.

Conclusions

The success of our QSAR to integrate, for bulk liquids, eye irritation data from the Draize test in rabbits, as MMAS values, with eye irritation thresholds in humans obtained by a standardized procedure has a number of very important implications. First, that for bulk liquids, there is a proven statistical and physicochemical basis to support the Draize test as an indirect measure of eye irritation thresholds in humans. Following on from this, we show that eye irritation thresholds in humans can be obtained by this indirect method for a large number of compounds that cannot be studied by the standardized procedure. These compounds include those that have too low a vapor pressure to elicit a response in humans, and those that cannot be studied on humans because of ethical considerations. Second, that the resulting QSAR represents the first time that such a scale having statistical significance, chemical diversity and physicochemical basis is available specifically for the eye irritation effect of vapors on humans.

A test, such as the Draize test, is certainly needed for eye irritancy of bulk liquids that might come into contact with the eye. However, we feel that consideration should be given to our scale as a new statistically sound measure of eye irritation of vapors on humans that could be used to assess the environmental impact of vapors.

We stress that although our QSAR covers a wide variety of compounds, there is still considerable scope for extending the range of compounds; this is part of an ongoing project to determine further values of eye irritation thresholds. The general QSAR, Eq. (7), has

proved also to be valuable in the analysis of odor thresholds in humans and nasal pungency (nasal irritation) thresholds in humans (Abraham *et al*., 2001; 2002b). Further work to extend the range of compounds in these two areas is ongoing, in the hope that we will be able to present a number of very general QSARs, not just the present one for eye irritation, that can be used for the prediction of environmental effects of vapors on humans.

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TABLE 1

Compounds, values of SP, and the compound descriptors [a]

Name	SP [a]	I	E	S	A	B	L	VG	LG	DP01
2-Bromobutane	-5.16	1	0.344	0.35	0.00	0.14	2.933	381.12	5.578	2.377
1-Bromo-4-chlorobutane	-3.34	1	0.571	0.82	0.00	0.25	4.007	436.15	6.906	2.839
Dichlorotoluenes (3,4)	-2.77	1	0.900	0.80	0.00	0.03	5.089	467.09	6.453	3.173
3,3-Dimethylpentane	-5.24	1	0.000	0.00	0.00	0.00	2.946	450.50	6.771	2.803
1-Bromooctane	-2.90	1	0.339	0.40	0.00	0.12	5.143	606.11	11.300	3.574
iso-Stearyl alcohol	2.37	1	0.140	0.39	0.37	0.48	9.500	1093.42	22.807	4.997
Methylisobutylketone	-3.73	1	0.111	0.65	0.00	0.51	3.089	421.84	6.221	2.833
3-Methylhexane	-5.06	1	0.000	0.00	0.00	0.00	3.044	470.70	8.009	2.938
4-Bromophenetole	-1.89	1	0.967	0.90	0.00	0.23	5.520	529.22	9.018	3.431
Di-n-propyl disulfide	-2.75	1	0.653	0.52	0.00	0.27	4.984	555.76	11.195	3.419
Heptyl methacrylate	-2.15	1	0.445	0.49	0.00	0.45	5.697	718.89	13.840	4.114
1-Bromohexane	-3.60	1	0.349	0.40	0.00	0.12	4.138	498.51	8.813	3.101
iso-Propyl iso-stearate	2.26	1	-0.020	0.53	0.00	0.47	10.250	1259.97	25.318	5.319
1-Bromopentane	-3.92	1	0.356	0.40	0.00	0.12	3.611	444.66	7.530	2.819
1,9-Decadiene	-3.17	1	0.184	0.20	0.00	0.10	4.380	617.13	13.018	3.753
1,6-Dibromohexane	-0.91	1	0.711	0.80	0.00	0.26	5.328	563.59	9.560	3.374
1,3-Diisopropylbenzene	-2.32	1	0.605	0.46	0.00	0.20	5.170	628.84	8.868	3.666
2-Methylpentane	-5.15	1	0.000	0.00	0.00	0.00	2.503	422.99	6.820	2.669
s-Butylbenzene	-3.08	1	0.603	0.48	0.00	0.16	4.506	528.60	8.173	3.369
3-Ethyltoluene	-3.23	1	0.630	0.51	0.00	0.18	4.275	484.64	7.785	3.187
Methyl trimethylacetate	-4.16	1	0.049	0.54	0.00	0.45	2.932	448.41	6.328	2.964
2-Bromopropane	-5.02	1	0.332	0.35	0.00	0.00	2.390	332.65	4.329	2.027
1,5-Dimethylcyclooctadiene	-2.90	1	0.604	0.30	0.00	0.18	4.812	533.10	7.843	3.330
cis-Cyclooctene	-3.48	1	0.460	0.24	0.00	0.10	4.119	446.17	5.699	2.949
iso-Stearic acid	4.38	1	0.015	0.57	0.60	0.49	9.600	1093.73	22.075	5.077

Methylcyclopentane	-4.69	1	0.225	0.10	0.00	0.00	2.907	385.83	5.271	2.509
Ethyl trimethylacetate	-3.55	1	-0.010	0.52	0.00	0.45	3.481	504.71	7.638	3.201
1,4-Dibromobutane	-2.00	1	0.733	0.80	0.00	0.27	4.353	455.93	7.084	2.856
1,5-Dibromopentane	-1.41	1	0.723	0.80	0.00	0.27	4.848	509.83	8.238	3.130
1,3-Dibromopropane	-2.89	1	0.723	0.80	0.00	0.27	3.872	402.12	5.741	2.542
iso-Myristyl alcohol	1.26	1	0.155	0.39	0.37	0.48	7.480	877.65	17.809	4.517
2,4-Difluoronitrobenzene	-1.83	1	0.677	1.20	0.00	0.25	4.350	408.66	6.315	3.446
1,5-Hexadiene	-4.80	1	0.191	0.15	0.00	0.10	2.450	402.30	8.039	2.762
4-Methylpentan-2-one	-3.73	1	0.111	0.65	0.00	0.51	3.089	426.79	6.831	2.845
Allyl methacrylate	-3.24	1	0.290	0.57	0.00	0.54	3.741	484.32	8.803	3.300
Styrene	-3.11	1	0.849	0.65	0.00	0.16	3.856	416.77	7.331	2.978
Butyl acetate [b]	-3.30	1	0.071	0.60	0.00	0.45	3.353	470.17	8.831	3.196
2,2-Dimethylpentan-3-ol	-2.70	1	0.227	0.27	0.31	0.60	3.400	474.04	6.855	2.989
Toluene [b]	-3.62	1	0.601	0.52	0.00	0.14	3.325	384.83	5.889	2.719
m-Xylene	-3.11	1	0.623	0.52	0.00	0.16	3.839	436.84	6.742	2.956
Heptan-2-one [b]	-2.68	1	0.123	0.68	0.00	0.51	3.760	489.92	9.321	3.229
2-Methylpentan-1-ol	-2.26	1	0.211	0.39	0.37	0.48	3.530	445.14	7.798	2.925
3-Choroproprionitrile	-2.65	1	0.387	1.22	0.02	0.40	3.070	321.06	5.105	2.440
Cellosolve acetate	-2.20	1	0.099	0.79	0.00	0.79	3.747	504.30	9.859	3.418
Ethyl acetate [b]	-3.91	1	0.106	0.62	0.00	0.45	2.314	361.36	6.375	2.606
Heptan-2-one [b]	-2.49	1	0.123	0.68	0.00	0.51	3.760	489.92	9.321	3.229
Ethyl 2-methylacetoacetate	-1.58	1	0.156	0.85	0.00	0.85	4.214	515.21	7.072	3.358
Cyclopentanol	-2.12	1	0.427	0.54	0.32	0.36	3.241	357.56	5.078	2.493
Ethanol [b]	-3.51	1	0.246	0.42	0.37	0.48	1.485	242.38	4.054	1.510
Methyl cyanoacetate	-0.78	1	0.291	1.34	0.00	0.64	3.367	353.43	6.454	2.849
Propan-2-ol	-3.27	1	0.212	0.36	0.33	0.56	1.764	293.20	4.326	1.929
Methyl acetate	-3.85	1	0.142	0.64	0.00	0.45	1.911	303.83	5.081	2.252
Octan-1-ol [b]	-0.39	1	0.199	0.42	0.37	0.48	4.619	565.90	11.552	3.548

g-Butyrolactone	-0.94	1	0.366	1.30	0.00	0.58	3.600	314.67	4.355	2.465
Furfuryl alcohol	-1.34	1	0.554	0.73	0.50	0.63	3.357	357.58	6.245	2.751
2,2-Dimethylbutanoic acid	-0.65	1	0.186	0.55	0.60	0.51	3.681	431.19	5.838	2.960
Methoxyethyl acrylate	-2.10	1	0.249	0.80	0.00	0.80	3.876	481.45	9.204	3.357
Pyridine	-2.75	1	0.613	0.84	0.00	0.52	3.022	318.53	4.941	2.428
Butanone	-3.38	1	0.166	0.70	0.00	0.51	2.287	328.03	5.595	2.291
2-Ethylhexan-1-ol	-0.57	1	0.209	0.39	0.37	0.48	4.433	546.11	8.886	3.344
iso-Butanol	-2.36	1	0.217	0.39	0.37	0.48	2.413	342.97	5.314	2.301
Butan-1-ol [b]	-2.13	1	0.224	0.42	0.37	0.48	2.601	350.58	6.554	2.423
Diethylaminopropriontrile	-0.83	1	0.267	0.89	0.00	0.86	4.479	515.76	7.571	3.337
Hexan-1-ol [b]	-1.13	1	0.210	0.42	0.37	0.48	3.610	457.78	9.053	3.061
Propanone [b]	-3.66	1	0.179	0.70	0.04	0.49	1.696	275.29	4.316	1.912
Ethyleneglycolmonobutyl ether	-1.32	1	0.201	0.50	0.30	0.83	3.806	491.96	10.074	3.289
4-Fluoroaniline	-1.06	1	0.760	1.09	0.20	0.40	4.007	376.72	6.105	2.950
Cyclohexanol	-1.00	1	0.460	0.54	0.32	0.57	3.758	398.55	4.889	2.704
Propanone [b]	-5.27	0	0.179	0.70	0.04	0.49	1.696	275.29	4.316	1.912
Pentan-2-one	-4.05	0	0.143	0.68	0.00	0.51	2.755	382.08	6.819	2.648
Heptan-2-one [b]	-2.49	0	0.123	0.68	0.00	0.51	3.760	489.92	9.321	3.229
Nonan-2-one	-2.35	0	0.119	0.68	0.00	0.51	4.735	597.48	11.813	3.686
Ethyl acetate [b]	-4.69	0	0.106	0.62	0.00	0.45	2.314	361.36	6.375	2.606
Butyl acetate [b]	-2.87	0	0.071	0.60	0.00	0.45	3.353	470.17	8.831	3.196
Hexyl acetate	-2.41	0	0.056	0.60	0.00	0.45	4.351	577.05	11.307	3.663
Octyl acetate	-2.02	0	0.029	0.60	0.00	0.45	5.364	684.18	13.795	4.043
Decyl acetate	-1.30	0	0.033	0.60	0.00	0.45	6.373	793.03	16.298	4.362
Ethanol [b]	-4.76	0	0.246	0.42	0.37	0.48	1.485	242.38	4.054	1.510
Propan-1-ol	-3.74	0	0.236	0.42	0.37	0.48	2.031	296.30	5.313	2.016
Butan-1-ol [b]	-3.37	0	0.224	0.42	0.37	0.48	2.601	350.58	6.554	2.423
Hexan-1-ol [b]	-2.60	0	0.210	0.42	0.37	0.48	3.610	457.78	9.053	3.061

Octan-1-ol [b]	-1.71	0	0.199	0.42	0.37	0.48	4.619	565.90	11.552	3.548
Toluene [b]	-4.41	0	0.601	0.52	0.00	0.14	3.325	384.83	5.889	2.719
Ethylbenzene	-3.87	0	0.613	0.51	0.00	0.15	3.778	432.04	7.284	2.981
Propylbenzene	-3.43	0	0.604	0.50	0.00	0.15	4.230	486.32	8.368	3.242
Cumene	-3.39	0	0.602	0.49	0.00	0.16	4.084	480.18	7.200	3.160
p-Cymene	-3.11	0	0.607	0.49	0.00	0.19	4.590	532.53	8.190	3.360
d-3-Carene	-3.30	0	0.511	0.22	0.00	0.10	4.649	529.88	7.470	3.280
Linalool	-2.55	0	0.398	0.55	0.20	0.67	4.794	613.77	10.000	3.680
1,8-Cineole	-2.15	0	0.383	0.33	0.00	0.76	4.688	543.92	6.400	3.330
Geraniol	-1.35	0	0.513	0.63	0.39	0.66	5.479	619.88	11.470	3.760
Dodecane	1.00	0	0.000	0.00	0.00	0.00	5.695			

[a] SP = log (MMAS/ P^o) when I = 1, and = log (1/EIT) when I = 0. [b] These are the nine common compounds in the two data sets.

Table 2

Prediction of SP values for the 46 compound test set from Eq. (10)

Statistic	Value
Average deviation, AD	-0.037
Average absolute deviation, AAD	0.345
Standard deviation	0.430

TABLE 3

Values of log Poct for some isomeric compounds (Leo, 2002)

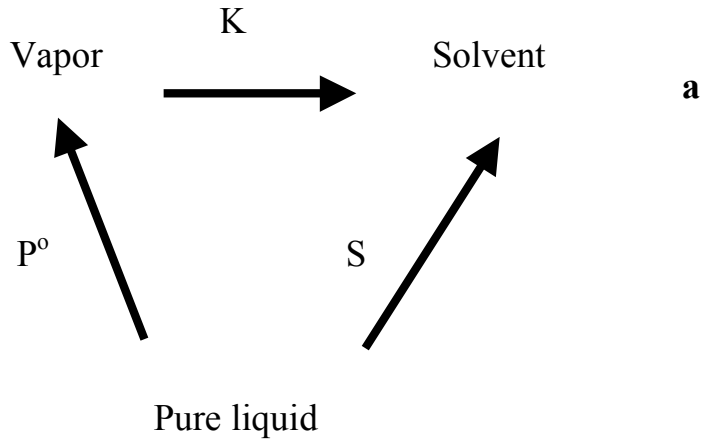
Compound		Compound		Compound	
Hexane	3.90	2-Methylpentane	3.73	2,2-Dimethylbutane	3.82
Hexan-1-ol	3.23	Hexan-2-ol	3.07	Hexan-3-ol	2.98
o-Methylphenol	1.97	m-Methylphenol	1.98	p-Methylphenol	1.97
o-Hydroxybenzamide	1.28	m-Hydroxybenzamide	0.39	p-Hydroxybenzamide	0.33

TABLE 4

Regression coefficients in Eq. (7) for gas-solvent (phase) partitions at 298K

Phase	*e*	*s*	*a*	*b*	*l*
Biophase, for EIT	-0.44	2.02	4.02	1.15	0.787
Water	0.82	2.73	3.90	4.81	-0.213
Wet 1-octanol	0.00	0.71	3.52	1.43	0.858
Wet chloroform	-0.47	1.20	0.14	1.43	0.994
Dry acetone	-0.27	1.52	3.26	0.08	0.863
Dry N,N'-dimethyl formamide	-0.19	2.33	4.76	0.00	0.808
Dry N-methylformamide	-0.26	2.06	4.56	0.43	0.706
Dry tetraethylene glycol	0.21	1.88	4.64	0.31	0.584
Plant matrix	0.08	1.28	3.12	0.82	0.860
Brain [a]	0.43	0.29	2.78	2.79	0.609
Muscle [a]	0.54	0.22	3.47	2.92	0.578
Plasma [a]	0.49	2.05	3.51	3.91	0.157

[a] At 310 K



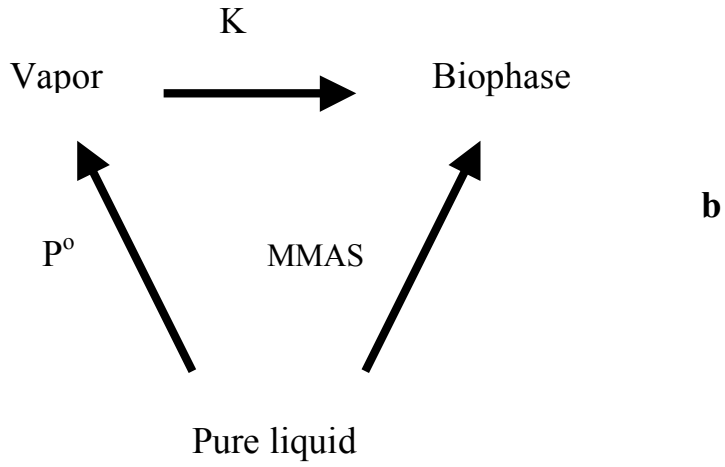


FIG. 1. The relationship between (a) liquid to vapor and liquid to solvent transfer and (b) liquid to vapor and liquid to biophase transfer. S is the solubility of a pure liquid in a solvent, P^o is the pure liquid saturated vapor pressure, K is the gas-to-solvent equilibrium constant and MMAS is the Draize eye score.

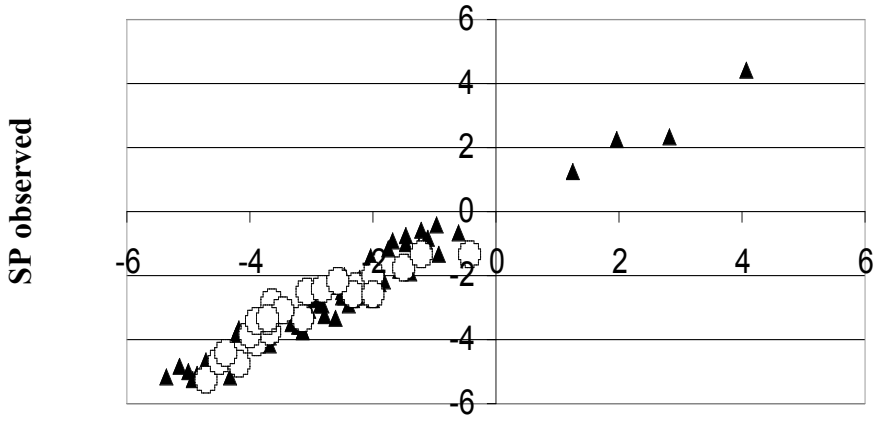


FIG. 2.. Plot of observed SP vs calculated SP on Eq.(8); SP = log (MMAS/ P^o) or log (1/EIT). ◆ log (MMAS/ P^o); 0 log (1/EIT).

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