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Draize Eye Scores and Eye Irritation Thresholds in Man Combined into one Quantitative Structure-Activity Relationship

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Running head: Draize scores and eye irritation thresholds

Abstract

Draize eye scores (DES) for 37 pure organic liquids have been converted into scores for the corresponding vapours, DES/P^o, where P^o is the liquid vapour pressure in ppm at 298 K. It is shown that there is a constant difference (0.66) between values of log(DES/P^o) and log(1/EIT) where EIT is the eye irritation threshold in ppm of eight vapours towards human subjects. The 37 log(DES/P^o) values can be combined with 17 log(1/EIT) values to give one quantitative structure-activity relationship,

$$\text{Log SP} = -7.918 - 0.482\ R_2 + 1.420\ \pi_2^H + 4.025\ \Sigma\alpha_2^H + 1.219\ \Sigma\beta_2^H + 0.853\ \log L^{16} \qquad [i]$$

$$n = 54,\ r^2 = 0.928,\ r_{CV}^2 = 0.913,\ sd = 0.36,\ F = 124$$

where R_2 is an excess molar refraction, π_2^H is the compound polarizability/dipolarity, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are the compound hydrogen-bond acidity and basicity, and L^{16} is the gas-hexadecane partition coefficient. The number of data points is n, the correlation coefficient is r, the standard deviation is sd, and F is the F-statistic. LogSP is then either [log(DES/P^o) - 0.66], or log(1/EIT). It is suggested that equation i can be used to predict eye irritation of organic vapours and pure liquids as eye irritation thresholds.

Abbreviations: DES = Draize eye scores; EIT = eye irritation threshold; VOCs = volatile organic compounds.

INTRODUCTION

A large number of physicochemical and biochemical processes that involve transfer of compounds from the vapour phase to a condensed phase have been correlated through the linear free energy relationship (LFER) shown in equation [1] (Abraham, 1994 and 1996),

$$\text{Log SP} = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \sum \alpha_2^H + b \cdot \sum \beta_2^H + l \cdot \log L^{16} \qquad [1]$$

Here (Abraham, 1994) logSP is the dependent variable and the compound, or solute, descriptors are R_2 an excess molar refraction, π_2^H the polarizability/dipolarity, $\sum \alpha_2^H$ and $\sum \beta_2^H$ the overall or effective hydrogen-bond acidity and basicity, and logL^{16} where L^{16} is the solute gas-hexadecane partition coefficient. It should be pointed out that these descriptors apply to solutes or compounds in dilute solution, and are not at all applicable to compounds as pure liquids. Equation [1] has been applied to a large number of processes in which solutes are transferred from the vapour phase to a condensed phase. These processes include gas-liquid chromatographic retention (Abraham et al., 1990; Kollie et al., 1992), the solubility of gases and vapours in water (Abraham et al., 1994) in organic solvents (Abraham et al., 1993) and in biological phases (Abraham and Weathersby, 1994), and the selection of phases for chemical sensors (McGill et al., 1994). Hence, equation [1] can now be regarded as an established equation for the correlation and interpretation of gas-to-condensed phase transport processes.

Descriptors in equation [1] are now available for several thousand compounds, so that any successful application of equation [1] to a biological process means that a very large number of predictions can automatically be made. This is important in the area of indoor air quality, where the presence of dozens of volatile organic compounds (VOCs), of unknown sensory properties, is suspected of evoking eye, nose and throat irritation–widely mentioned symptoms in problematic indoor environments (Cometto-Muñiz and Cain, 1992). Recently, human nasal pungency (irritation) thresholds have been systematically gathered for a number of VOCs (Cometto-Muñiz and Cain, 1990, 1991, 1993 and 1994; Cometto-Muñiz et al., 1997a,b). We have been able to apply equation [1] to these human nasal pungency thresholds (NPT in ppm) for 43 varied VOCs, yielding the quantitative structure-activity relationship (QSAR) shown as equation [2] (Abraham et al., 1996)

$$\text{Log}(1/\text{NPT}) = -8.519 + 2.154 \, \pi_2^H + 3.522 \sum \alpha_2^H + 1.397 \sum \beta_2^H + 0.860 \log L^{16} \qquad [2]$$

$$n = 43, \, r^2 = 0.955, \, sd = 0.272, \, F = 201$$

The number of solutes (VOCs) is denoted as n, the correlation coefficient as r, the standard error as sd, and the F-statistic as F. Although equation [2] needs to

be expanded by the incorporation of additional VOCs, if possible, it is already a useful equation for the prediction of further values of nasal pungency thresholds in human subjects.

MATERIALS AND METHODS

Eye irritation thresholds in humans (EIT in ppm) have been gathered for 17 VOCs, see Table 1 (Cometto-Muñiz and Cain, 1991 and 1995; Cometto-Muñiz et al., 1998). Unlike the case of nasal irritation thresholds, there is neither the number nor the variety of compound type to carry out an analysis on the log(1/EIT) values using equation [1].

Table 1. Eye irritation thresholds, EIT, in human subjects

Compound	EIT/ppm	log(1/EIT)
Ethanol	57,580	−4.76
Propan-1-ol	6980	−3.84
Butan-1-ol	2330	−3.37
Hexan-1-ol	514	−2.71
Octan-1-ol	60	−1.78
Ethyl acetate	48,810	−4.69
Butyl acetate	737	−2.87
Hexyl acetate	256	−2.41
Octyl acetate	105	−2.02
Decyl acetate	20	−1.30
Propanone	186,260	−5.27
Pentan-2-one	11,180	−4.05
Heptan-2-one	311	−2.49
Nonan-2-one	224	−2.35
Toluene	25,780	−4.41
Ethylbenzene	7408	−3.87
Propylbenzene	2682	−3.43

We therefore sought to combine the eye irritation results on humans with Draize eye scores on rabbits (DES). The latter refer to the effect of pure liquid compound, and so are not directly comparable with the effect of vapour irritants. However, we previously used a stratagem for transforming DES for liquids (Cronin et al., 1994) into scores for the corresponding vapours through equation [3] (Abraham et al., 1997)

$$\text{Log}(DES/P^o) = \log L \qquad [3]$$

where P^o is the vapour pressure of the liquid (in ppm at 298 K), and L is then an Ostwald solubility coefficient for the transfer of the irritant vapour from the gas phase to the condensed biophase, with L defined through equation [4],

$$L = \frac{[\text{concn of the solute in the condensed phase}]}{[\text{concn of the solute in the gas phase}]} \qquad [4]$$

Application of equation [1] to values of $\log(DES/P^o)$ for 37 compounds led to the QSAR (Abraham et al., 1997)

$$\log(DES/P^o) = -6.955 + 1.046\ \pi_2^H + 4.437\ \textstyle\sum\alpha_2^H + 1.350\ \textstyle\sum\beta_2^H + 0.754\ \log L^{16} \qquad [5]$$

$$n = 37,\ r^2 = 0.951,\ sd = 0.32,\ F = 155.9$$

The 37 compounds, with values of DES, $\log P^o$ and $\log(DES/P^o)$ are in Table 2. In order to combine the EIT values with the values of DES/P^o, it is not necessary for the two sets of data to be numerically the same; all that is required is a method of matching the two scales of irritation. In Table 3 are values of $\log(DES/P^o)$ and $\log(1/EIT)$ for eight common solutes. We use $\log(1/EIT)$ rather than $\log(EIT)$ so that the more potent is the VOC, the larger numerically is $\log(1/EIT)$. For the eight VOCs, the average difference in the two measures of potency is 0.7 log units with considerable variation. As the standard error in the $\log(DES)$ values is almost one log unit (Balls et al., 1995), we do not expect any better agreement. However, we can say that there is some match between $\log(DES/P^o)$ and $\log(1/EIT)$.

To examine this further, we can use equation [5] to calculate $\log(DES/P^o)$ values for the 17 compounds in Table 1, and can then compare these calculated values with the given $\log(1/EIT)$ values. We find that the average for $\log(DES/P^o)_{calc} - \log(1/EIT)_{obs}$ is 0.63, so that we can subtract 0.63 units from the $\log(DES/P^o)$ values and then use these amended values with the $\log(1/EIT)$ values in equation [1] itself.

We now have 54 data points, namely 37 values of $\log(DES/P^o)$ and 17 of $\log(1/EIT)$. The required descriptors for the 54 compounds have been published previously (Abraham 1994; Abraham et al., 1997).

The statistical packages and methods used to solve the multiple linear regression equations, and to identify any possible outliers, were exactly those described earlier (Abraham et al., 1997).

Table 2. Draize eye scores as log(DES), vapour pressures as logP^o/ppm, and values of log(DES/P^o)

Compound	logDES	logP^o	log(DES/P^o)
Methyl trimethylacetate	0.43	4.59	−4.16
Ethyl trimethylacetate	0.62	4.13	−3.51
Butyl acetate	0.88	4.18	−3.30
Ethyl acetate	1.18	5.09	−3.92
Cellosolve acetate	1.18	3.38	−2.21
Ethyl 2-methylacetoacetate	1.26	2.84	−1.58
Methyl acetate	1.60	5.45	−3.86
2,2-Dimethylbutanoic acid	1.65	2.30	−0.64
Glycerol	0.22	−0.63	0.86
Propan-1-ol	1.48	4.75	−3.27
2-Ethylhexan-1-ol	1.70	2.28	−0.58
Isobutanol	1.78	4.14	−2.36
Butan-1-ol	1.78	3.91	−2.13
Hexan-1-ol	1.81	2.94	−1.13
Butyl cellosolve	1.84	3.16	−1.33
Cyclohexanol	1.90	2.90	−1.00
4-Bromophenetole	0.12	2.00	−1.88
1,3-Diisopropylbenzene	0.30	2.62	−2.32
sec-Butylbenzene	0.30	3.38	−3.08
3-Ethyltoluene	0.37	3.59	−3.22
2,4-Difluoronitrobenzene	0.56	2.50	−1.94
Styrene	0.83	3.94	−3.11
Toluene	0.95	4.57	−3.62
m-Xylene	0.95	4.06	−3.11
4-Fluoroaniline	1.84	2.90	−1.06
3-Methylhexane	−0.17	4.91	−5.08
2-Methylpentane	0.30	5.45	−5.14
1,9-Decadiene	0.30	3.47	−3.17
Dodecane	0.30	2.19	−1.89
1,5-Dimethylcyclooctadiene	0.45	3.35	−2.90
cis-Cyclooctene	0.52	4.00	−3.48
Methylcyclopentane	0.56	5.26	−4.69
Hexa-1,5-diene	0.67	5.47	−4.80
Methyl isobutyl ketone	0.68	4.41	−3.73
Heptan-2-one	1.21	3.70	−2.49
Butanone	1.70	5.08	−3.38
Propanone	1.82	5.48	−3.67

Table 3. Values of log(DES/P^o) and log(1/EIT) for eight common compounds

Compound	log(DES/P^o)	log(1/EIT)	Difference
Butan-1-ol	−2.13	−3.37	1.24
Hexan-1-ol	−1.13	−2.71	1.58
Ethyl acetate	−3.92	−4.69	0.77
Butyl acetate	−3.30	−2.87	−0.43
Propanone	−3.67	−5.27	1.60
Heptan-2-one	−2.49	−2.49	0.00
Toluene	−3.62	−4.41	0.79
Propylbenzene	−3.22[a]	−3.43	0.21
Average			0.72

[a]Value for 3-ethyltoluene.

<div align="center">RESULTS</div>

We began by using [log(DES/P^o) − 0.63] and log(1/EIT) as the dependent variable in equation [1], but found that a small adjustment to 0.66 units gave the better equations [6] and [7].

$$logSP = - (7.918 \pm 0.211) - (0.482 \pm 0.307)R_2 + (1.420 \pm 0.376)\pi_2^H + (4.025 \pm 0.404)\sum\alpha_2^H + (1.219 \pm 0.455)\sum\beta_2^H + (0.853 \pm 0.048) \log L^{16} \qquad [6]$$

$$n = 54, \ r^2 = 0.928, \ r_{CV}^2 = 0.913, \ sd = 0.363, \ F = 123.8$$

$$logSP = - (7.943 \pm 0.213) + (1.017 \pm 0.278)\pi_2^H + (3.685 \pm 0.346)\sum\alpha_2^H + (1.713 \pm 0.333)\sum\beta_2^H + (0.838 \pm 0.048) \log L^{16} \qquad [7]$$

$$n = 54, \ r^2 = 0.924, \ r_{CV}^2 = 0.910, \ sd = 0.368, \ F = 149.6$$

In equations [6] and [7] the sd values for the coefficients are also given. In Fig. 1 is shown a plot of observed v. calculated logSP values on equation [7], where the dependent variable is either [log(DES/P^o) − 0.66] or log(1/EIT).
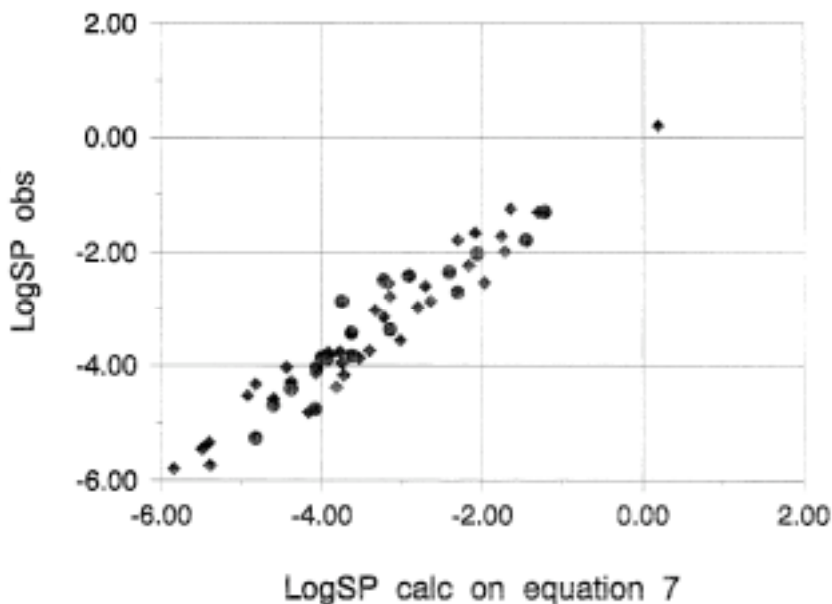

Fig. 1. Plot of logSP observed vs logSP calculated on equation [7]; Draize test compounds (diamonds), eye irritation compounds (circles).

In setting out equations [6] and [7], it is important that there should be no strong cross-correlations between the descriptors. The matrix in r^2 is given below, and shows that for the 54 VOCs we have studied there is very little cross-correlation.

	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$
π_2^H	0.093			
$\Sigma\alpha_2^H$	0.000	0.000		
$\Sigma\beta_2^H$	0.086	0.276	0.270	
$\log L^{16}$	0.078	0.006	0.046	0.038

DISCUSSION

Equations [6] and [7] encompass two quite different measures of eye irritation, the Draize eye test on rabbits and the eye irritation thresholds of Cometto-Muñiz and Cain, on human subjects. To our knowledge this is the first time that the *in vivo* Draize eye test scores have been satisfactorily matched to any other *in vivo* test at all, let alone to tests on human subjects. The success of equations [6] and [7] confirms that the Draize eye scores can be matched to the EIT values as we calculated for the compounds in Table 1. As equations [6] and [7] are based on the concept of transport of VOCs from the vapour phase to a condensed phase, since the statistics are so good, and because there are no outliers in the 54 data points, we strongly suggest that for the compounds listed in Tables 1 and 2, the main feature of both the Draize test and the eye irritation thresholds is simply transport of the compound into the biophase. There is no need to postulate different mechanisms of action for different types of compound at all. Of course, we do not suggest that all compounds (in the form of pure liquids in the Draize test or vapours in the threshold test) will exert irritation through a transport driven process, but only that for the compounds in Tables 1 and 2, this is the major process.

The coefficients in equations [6] and [7] refer to properties of the biophase, and in Table 4 we summarize the characteristic coefficients in equation [1] for a number of processes in which solutes are transferred from the vapour phase to a condensed phase (Abraham, 1996; Abraham and Weathersby, 1994). From the values listed, it seems as though transfer from the vapour phase to wet octanol might be a very good model for the eye irritation thresholds, and we hope to pursue this when we have assembled a large data base of logL(octanol) values. What we can deduce already is that the biophase is polarizable/dipolar (s= 1.42), a strong hydrogen-bond base (a= 4.02) comparable to a phosphate ester or an amide, a moderate-to-weak hydrogen-bond acid comparable to wet octanol or to chloroform (b =1.22), and of average hydrophobicity (l = 0.85). Such a comparison shows also that the coefficients in equations [6] and [7] are chemically reasonable, and are just not arbitrary fitting coefficients.

Table 4. Coefficients in equation [1] for transfer of solutes from the vapour phase to condensed phases

Phase	logSP	r	s	a	b	l
Water (37°C)	logL	1.05	2.63	3.74	4.50	−0.25
NFM (25°C)[a]	logL	–	2.57	4.32	–	0.73
NFM (40°C)	logL	–	2.39	3.92	–	0.68
EHP (25°C)[b]	logL	−0.26	0.91	3.74	–	0.95
EHP (37°C)	logL	−0.19	0.83	3.41	–	0.89
OCT (25°C)[c]	logL	–	0.62	3.73	1.36	0.86
Oil (37°C)[d]	logL	−0.02	0.81	1.47	–	0.89
CHCl$_3$ (25°C)	logL	−0.35	1.26	0.60	1.18	0.99
Hexadecane	logL	0.00	0.00	0.00	0.00	1.00
Nasal pungency	log(1/NPT)	–	2.15	3.52	1.40	0.86
Draize scores	log(DES/P°)	–	1.05	4.44	1.35	0.75
Eye irritation	Eq.6	−0.48	1.42	4.02	1.22	0.85

[a] N-Formylmorpholine.
[b] Tri-(2-ethylhexyl) phosphate.
[c] Wet octanol.
[d] Olive oil.

We can now use the constant difference of 0.66 log units to convert the experimental EIT scores into DES values through log(DES/P°) = [log(1/EIT)obs + 0.66]. Alternatively, we can predict DES values through equation [7] with the descriptors given before (Abraham 1994; Abraham et al., 1997). A knowledge of EIT values is not necessary in order to predict DES values; these can be obtained straight from equation [7] as [log(SP)calc + 0.66], for any VOC for which descriptors are available.

The reverse calculation of EIT is simpler, using either log(1/EIT) = [log(DES/P°)obs - 0.66] or log(1/EIT) = log(SP)calc on equation [7]. Results are in Table 5, given as log(1/EIT) because of the large spread in EIT values. The calculation based on equation [7] seems the better, and this could be used to predict EIT values, especially in cases where it is difficult to measure the eye irritation thresholds experimentally. These cases include the alkanes with very low potency, and VOCs with low vapour pressure such as glycerol and 4-bromophenetole.

In conclusion, we have shown that Draize eye scores, when corrected from pure liquid to vapour, can be matched to eye irritation thresholds in human subjects, we have obtained a correlation equation that can be used to predict further eye irritation thresholds, we have shown that for the particular data set the main process in the two biological tests is transfer of the irritant from the vapour to the biophase, and we have mapped out some of the chemical properties of the biological phase itself.

Table 5. Prediction of eye irritation thresholds

Compound	pred log(1/EIT)[a]	pred log(1/EIT)[b]	obs log(1/EIT)[c]
Methyl trimethylacetate	−4.82	−4.17	
Ethyl trimethylacetate	−4.17	−3.73	
Butyl acetate	−3.96	−3.75	−2.87
Ethyl acetate	−4.58	−4.60	−4.69
Cellosolve acetate	−2.87	−2.65	
Ethyl 2-methylacetoacetate	−2.24	−2.17	
Methyl acetate	−4.52	−4.92	
2,2-Dimethylbutanoic acid	−1.30	−1.31	
Glycerol	0.20	0.19	
Propan-2-ol	−3.93	−3.92	
2-Ethylhexan-1-ol	−1.24	−1.65	
Isobutanol	−3.02	−3.34	
Butan-1-ol	−2.79	−3.15	−3.37
Hexan-1-ol	−1.79	−2.30	−2.71
Butyl cellosolve	−1.99	−1.72	
Cyclohexanol	−1.66	−2.09	
4-Bromophenetole	−2.54	−1.97	
1,3-Diisopropylbenzene	−2.98	−2.80	
sec-Butylbenzene	−3.74	−3.41	
3-Ethyltoluene	−3.88	−3.53	−3.43[c]
2,4-Difluoronitrobenzene	−2.60	−2.71	
Styrene	−3.77	−3.78	
Toluene	−4.28	−4.39	−4.41
m-Xylene	−3.77	−3.84	
4-Fluoroaniline	−1.72	−1.76	
3-Methylhexane	−5.74	−5.39	
2-Methylpentane	−5.80	−5.85	
1,9-Decadiene	−3.83	−3.90	
Dodecane	−2.55	−3.17	
1,5-Dimethylcyclooctadiene	−3.56	−3.02	
cis-Cyclooctene	−4.14	−4.08	
Methylcyclopentane	−5.35	−5.41	
Hexa-1,5-diene	−5.46	−5.49	
Methyl isobutyl ketone	−4.39	−3.82	
Heptan-2-one	−3.15	−3.22	−2.49
Butanone	−4.04	−4.44	
Propanone	−4.33	−4.82	−5.27

[a]Log(1/EIT) = log(DES/P°)obs−0.66.
[b]Log(1/EIT) = log(SP), calc through equation [7].
[c]Value for propylbenzene.

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