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An algorithm for nasal pungency thresholds in man

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Abstract

Nasal pungency thresholds (NPT) in man have been determined by Cometto-Muñiz and Cain for 44 varied compounds, including esters, aldehydes, ketones, alcohols, carboxylic acids, aromatic hydrocarbons and pyridine. With the exclusion of acetic acid, 43 of these NPT values are well correlated through the general linear free energy equation of Abraham, leading to the algorithm,

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

$$n = 43,\ r^2 = 0.955,\ \mathrm{SD} = 0.27,\ F = 201$$

where the independent variables are solute descriptors: π_2^H is the dipolarity/polarizability, $\sum\alpha_2^H$ and $\sum\beta_2^H$ are the overall or effective hydrogen-bond acidity and basicity, and L^{16} is the solute Ostwald solubility coefficient on hexadecane at 25 °C. Surprisingly, the aliphatic aldehydes and carboxylic acids fit the correlation and with respect to nasal pungency thresholds in man for brief (1-3 s) presentations must be regarded as `nonreactive' compounds. It is suggested mere transport of the compound from the air stream to the receptor area largely determines the potency to produce pungency. Various chemical properties of the receptor area are deduced from the coefficients in Eq. i.

Keywords: Nasal pungency · Sensory irritation · Volatile organic compounds · Hydrogen bonding · Linear free energy equation

Introduction

Volatile organic compounds (VOCs) are of crucial importance as regards air quality, especially indoor air quality. Most people spend 70 to 90% of their time indoors, where the concentration of VOCs in the atmosphere is typically from 2 to 20 times greater than concentrations found outdoors (Brown et al. 1994). The perceived effect of VOCs can broadly be divided into odour and sensory irritation, the latter being so important that 40% of the workplace threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists are based on this effect (Alarie1981). Sensory irritation includes both nasal pungency and eye irritation (Cometto-Muñiz and Cain 1995). Hence bioassays for nasal pungency are particularly relevant to the assessment of indoor air quality. The VOCs that could be encountered at the workplace or in the home number several thousand. In nonindustrial buildings the number is less, although several hundred VOCs have been identified (Berglund et al.1986). These figures contrast with the number of VOCs actually tested. Nasal pungency thresholds of VOCs in man have been obtained for only 44 VOCs (Cometto-Muñiz and Cain 1990, 1991, 1992, 1993, 1994; Cometto-Muñiz et al. 1997). These may be supplemented by use of the mouse bioassay (Alarie 1966), which is now an American Society for Testing and Materials (ASTM) standard method (ASTM 1984); however, values for only 150 VOCs were listed in a recent comprehensive review (Schaper 1993). There is thus an urgent need for some method of estimating sensory irritation, and in this paper we set out to develop a predictive algorithm for nasal pungency thresholds in man.

Materials and methods

We use the general linear free energy relationship (LFER) or quantitative structure-activity relationship (QSAR) given in Eq. 1 (Abraham 1993):

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

Here, the dependent variable log SP is some property of a series of compounds (solutes) in a given phase system. For nasal pungency thresholds we shall take log SP as log(1/NPT) where NPT is the nasal pungency threshold in ppm; we use log(1/NPT) in order that the larger this quantity, the more potent is the irritant. For the solubility of gases and vapours in solvent phases and biological phases, log SP is taken as log L where L is the Ostwald solubility coefficient defined by Eq. 2; L is identical to the gas-phase partition coefficient, K. Thus:

L = [conc. of solute in phase] / [conc. of solute in gas] (2)

The independent variables in Eq. 1 are (Abraham 1993): R_2 an excess molar refraction, π_2^H the dipolarity/polarizability, $\sum\alpha_2^H$ and $\sum\beta_2^H$ the overall or effective hydrogen-bond acidity and basicity, and log L^{16} where L^{16} is the solute Ostwald solubility coefficient on hexadecane at 25 °C. The coefficients c, r, s, a, b, and l are found by multiple linear regression analysis. However, these are not simply fitting coefficients, because they reflect the complementary properties of the solvent phase or biophase. The r-coefficient gives the tendency of the phase to interact with gaseous solutes through polarizability-type interactions, mostly via electron pairs. This coefficient is usually small and positive for aromatic phases but is sometimes negative for phases that contain halogen atoms and some polar phases as well. The s-coefficient is a measure of the phase dipolarity/polarizability and must always be positive. The a-coefficient represents the complementary property to solute hydrogen-bond acidity and thus is a measure of the phase hydrogen-bond basicity. Likewise, the b-coefficient is a measure of the phase hydrogen-bond acidity. The l-coefficient is a combination of the work needed to create a cavity in the phase (leading to a negative coefficient) and the general dispersion interaction energy between solute and phase (leading to a positive coefficient). For all phases except water, the dispersion interaction dominates and the l-coefficient is positive.

Equation 1 has been applied to numerous sets of gas chromatographic data (Kollie et al. 1992), to the assessment of phases for chemical sensors (McGill et al. 1994), and to the solubility of gases and vapours in water (Abraham et al. 1994a) and organic solvents (Abraham et al. 1994b). It is therefore a well-tested and well-used equation. As examples of the application of Eq. 1, we give in Table 1 results for the solubility of gases and vapours in a variety of solvents (Abraham et al. 1994b) and biological systems (Abraham and Weathersby 1994). As required, the s-, a-, and b- coefficients are all positive, with water acting as the most dipolar, most basic and most acidic phase of those listed. Equation 1 has also been applied to a less complete set of log(1/NPT) values, viz. the first 34 compounds in Table 2 (Abraham et al. 1996):

$$\log(1/NPT) = -8.562 + 2.209\,\pi_2^H + 3.417\,\sum\alpha_2^H + 1.535\,\sum\beta_2^H + 0.865\,\log L^{16} \qquad (3)$$

$$n = 34,\ r^2 = 0.953,\ SD = 0.27,\ F = 144$$

Here, n is the number of data points, r is the correlation coefficient, SD is the standard deviation in the dependent variable, and F is the F-statistic. The r-coefficient of the independent variable R_2 was statistically not significant.

Table 1 Coefficients in Eq. 1 for the solubility of gases and vapours in solvent phases and biological phases at 37 °C. (*NFM* N-Formylmorpholine at 40 °C, *EHP* tri-(2-ethylhexyl)-phosphate, *NPT* nasal pungency threshold)

Phase	*c*	*r*	*s*	*a*	*b*	*l*
Water	−1.36	1.06	2.63	3.74	4.50	−0.245
Blood	−1.27	0.61	0.92	3.61	3.38	0.362
Fat	−0.29	−0.17	0.73	1.75	0.22	0.895
Olive oil	−0.24	−0.02	0.81	1.47	0.00	0.891
NFM	−0.56	0.00	2.39	3.92	0.00	0.676
EHP	−0.09	−0.19	0.83	3.41	0.00	0.889
NPT[a]	–	0.07	2.15	3.52	1.46	0.863
NPT[b]	–	–	2.15	3.52	1.40	0.860

[a] LogSP = log(1/NPT), Eq. 4
[b] LogSP = log(1/NPT), Eq. 5

Results and discussion

An algorithm for NPTs

The nasal pungency thresholds that we use are given in Table 2, as log(1/NPT) with NPT in ppm. The most recent values are for the aldehydes and carboxylic acids (Cometto-Muñiz et al. 1997). The VOC descriptors are also in Table 2 and with one exception are exactly as given previously (Abraham 1993). The exception is formic acid for which R_2 was calculated from the refractive index as described before (Abraham et al. 1990), the descriptors π_2^H , $\sum\alpha_2^H$, and $\sum\beta_2^H$ were calculated from water-solvent partitions as explained in detail (Abraham and Chadha 1996), and the log L^{16} descriptor was estimated from calculated gas-water and water-hexadecane partition coefficients.

As a first step, we can test the predictive capability of Eq. 3 using the new values of NPT obtained (Cometto-Muñiz et al. 1997; see Table 3). With the exception of acetic acid, there is very good agreement between log(1/NPT) calculated via Eq. 3 and the observed values. The aldehydes, especially the lower homologs which were not tested in humans, and the carboxylic acids are regarded as `reactive' irritants in the mouse bioassay (Alarie et al. 1997), but appear to be `nonreactive' as regards NPT values in man. However, there are important differences in exposure time and exposed surface area between the mouse bioassay and the human NPTs. Both of these factors have been shown to play an important role in the perception of nasal

irritation (Garcia-Medina and Cain 1982; Cometto-Muñiz and Cain 1984). In the mouse bioassay, mice have their whole head exposed to the stimulus for ≥10 min, but in the NPT test, humans are presented with a brief stimulus puff (1-3 s) to one nostril only. Possibly, the aldehydes and acids are `nonreactive' for presentations that are brief and surface restricted. In any case, since the aldehydes and acids conform to Eq. 3, we can construct a much more general QSAR using all the VOCs in Table 2, except acetic acid:

$$\log(1/\mathrm{NPT}) = -8.561 + 0.066\,R_2 + 2.145\,\pi_2^H + 3.515\,\sum\alpha_2^H + 1.460\,\sum\beta_2^H + 0.863\,\log L^{16} \qquad (4)$$

$$n = 43,\ r^2 = 0.955,\ \mathrm{SD} = 0.28,\ F = 157$$

Table 2 Descriptors, as defined in Eq. 1, and values of log(1/NPT) for volatile organic compounds (VOCs)

VOC	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	$\log L^{16}$	log(1/NPT)
Oct-1-yne	0.155	0.23	0.12	0.10	3.521	−4.49
Propanone	0.179	0.70	0.04	0.49	1.696	−5.12
Pentan-2-one	0.143	0.68	0.00	0.51	2.755	−3.47
Heptan-2-one	0.123	0.68	0.00	0.51	3.760	−2.91
Nonan-2-one	0.119	0.68	0.00	0.51	4.735	−2.53
Methyl acetate	0.142	0.64	0.00	0.45	1.911	−5.05
Ethyl acetate	0.106	0.62	0.00	0.45	2.314	−4.83
Propyl acetate	0.092	0.60	0.00	0.45	2.819	−4.24
Butyl acetate	0.071	0.60	0.00	0.45	3.353	−3.56
s-Butyl acetate	0.044	0.57	0.00	0.47	3.054	−3.60
t-Butyl acetate	0.025	0.54	0.00	0.47	2.802	−3.98
Pentyl acetate	0.067	0.60	0.00	0.45	3.844	−3.22
Hexyl acetate	0.056	0.60	0.00	0.45	4.351	−2.80
Heptyl acetate	0.050	0.60	0.00	0.45	4.865	−2.49
Octyl acetate	0.029	0.60	0.00	0.45	5.364	−1.95
Decyl acetate	0.033	0.60	0.00	0.45	6.373	−0.70
Dodecyl acetate	0.012	0.60	0.00	0.45	7.381	−0.10
Methanol	0.278	0.44	0.43	0.47	0.970	−4.53
Ethanol	0.246	0.42	0.37	0.48	1.485	−3.91
Propan-1-ol	0.236	0.42	0.37	0.48	2.031	−3.49
Propan-2-ol	0.212	0.36	0.33	0.56	1.764	−4.26
Butan-1-ol	0.224	0.42	0.37	0.48	2.601	−3.20
s-Butanol	0.217	0.36	0.33	0.56	2.338	−3.76
t-Butanol	0.180	0.30	0.31	0.60	1.963	−4.52
Pentan-1-ol	0.219	0.42	0.37	0.48	3.106	−3.21
Hexan-1-ol	0.210	0.42	0.37	0.48	3.610	−2.62
Heptan-1-ol	0.211	0.42	0.37	0.48	4.115	−2.32
Heptan-4-ol	0.180	0.36	0.33	0.56	3.850	−2.53
Octan-1-ol	0.199	0.42	0.37	0.48	4.619	−1.99
Toluene	0.601	0.52	0.00	0.14	3.325	−4.47
Ethylbenzene	0.613	0.51	0.00	0.15	3.778	−4.00
Propylbenzene	0.604	0.50	0.00	0.15	4.230	−3.17
Chlorobenzene	0.718	0.65	0.00	0.07	3.657	−4.02
Pyridine	0.631	0.84	0.00	0.52	3.022	−3.11
Butanal	0.187	0.65	0.00	0.45	2.270	−4.77
Pentanal	0.163	0.65	0.00	0.45	2.851	−4.57
Hexanal	0.146	0.65	0.00	0.45	3.357	−3.70
Heptanal	0.140	0.65	0.00	0.45	3.865	−3.13
Octanal	0.160	0.65	0.00	0.45	4.361	−3.24
Formic acid	0.300	0.79	0.72	0.34	1.400	−2.50
Butanoic acid	0.210	0.62	0.60	0.45	2.830	−1.79
Hexanoic acid	0.174	0.60	0.60	0.45	3.920	−1.30
Octanoic acid	0.150	0.60	0.60	0.45	5.000	−0.30
Acetic acid	0.265	0.65	0.61	0.44	1.750	−1.62

Table 3 Observed and predicted values of log(1/NPT) as obtained via Eq. 3 and Eq. 5 for aldehydes and carboxylic acids

VOC	log(1/NPT)		
	Observed	Predicted[a]	Calculated[b]
Butanal	−4.77	−4.47	−4.54
Pentanal	−4.57	−3.97	−4.04
Hexanal	−3.70	−3.53	−3.60
Heptanal	−3.13	−2.66	−3.16
Octanal	−3.24	−2.62	−2.73
Formic acid	−2.50	−2.62	−2.60
Acetic acid	−1.62	(−2.85)	(−2.85)
Butanoic acid	−1.79	−2.00	−2.01
Hexanoic acid	−1.30	−1.11	−1.11
Octanoic acid	−0.30	−0.17	−0.18

[a] From Eq. 3
[b] From Eq. 5

As before, the $r \cdot R_2$ term is not statistically significant, and if that is omitted we find:

$$\log(1/NPT) = -(8.519 \pm 0.274) + (2.154 \pm 0.343)\,\pi_2^H + (3.522 \pm 0.215)\,\sum\alpha_2^H + (1.397 \pm 0.355)\,\sum\beta_2^H + (0.860 \pm 0.034)\log L^{16} \quad (5)$$

$$n = 43,\ r^2 = 0.955,\ SD = 0.27,\ F = 201$$

For completeness in Eq. 5, we give the standard deviation in each coefficient. The goodness-of-fit of Eq. 5 is excellent. The standard deviation in log(1/NPT) is only 0.27 log units in a range of 5 log units overall, and a plot of observed values of log(1/NPT) vs those calculated from Eq. 5 shows only random scatter about the line of identity (see Fig. 1). Although the coefficients in Eq. 5 are the same as those in the original Eq. 3, within experimental error, we much prefer the new Eq. 5 as an algorithm for the estimation of nasal pungency thresholds. Not only are there more data points, but the range of the $\sum\alpha_2^H$ descriptor has been altered from 0.43 to 0.72, a very considerable increase. In Table 3 we give also the calculated log(1/NPT) values for the aldehydes and carboxylic acids from Eq. 5; as expected there is just as good agreement with observed values as for the predicted log(1/NPT) values from Eq. 3.

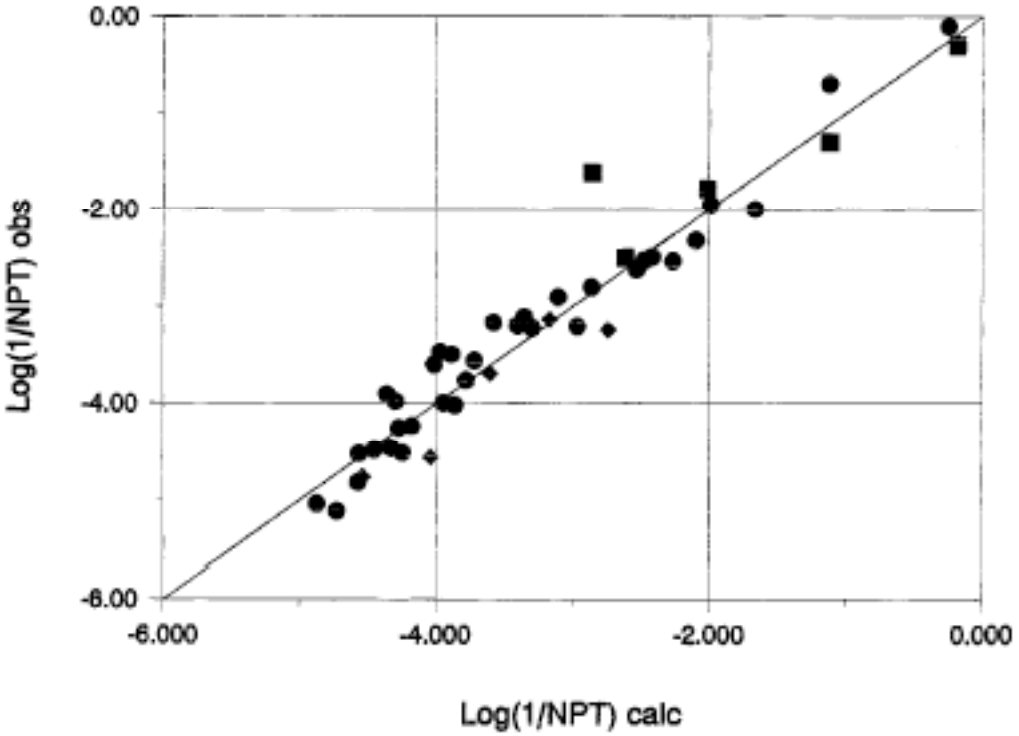

Fig. 1 Plot of log(1/NPT) observed vs log(1/NPT) calculated from Eq. 5. ◆ Aldehydes, ■ carboxylic acids; note the outlying point for acetic acid

We regard it as highly significant that aldehydes and carboxylic acids are included in the QSAR, Eq. 5. Thus, as regards nasal pungency thresholds for brief (1±3 s) presentations, these VOCs would be regarded as nonreactive compounds. One considerable difficulty over predictions of the mouse bioassay RD_{50} end-point, is that there are a number of reactive chemical types for which equations such as Eq. 1 always lead to a predicted potency much less than observed (Alarie et al. 1997). Such reactive VOCs include not only aldehydes and carboxylic acids, but allylic compounds, amines, isocyanates and the benzyl halides. If it turns out that even more of the VOCs that are reactive in the mouse bioassay are nonreactive in the NPT experiments, predictions of NPT values would be enabled to be made much more easily through the algorithm, Eq. 5. A useful way to distinguish between reactive and nonreactive compounds is through a logarithmic plot of biological response, BR, against the saturated vapour pressure, Po. Although there is no rigorous thermodynamic basis for any linear relationship between logBR and $logP^o$, the Ferguson rule is often obeyed (Abraham et al. 1994b). Values of $log(P^o)$ with P^o in ppm at 25 °C are given in Table 4; 10^6 ppm = 1 atmosphere. It would make little difference if vapour pressures at 37 °C were used, but many compilations list 25 °C values. For the same 43 VOCs used in Eq. 5:

$$\text{Log}(1/\text{NPT}) = 0.314 \pm 0.941 \log(1/P^o) \quad (6)$$

n = 43, r2 = 0.880, SD = 0.43, F = 302

Table 4 VOC vapour pressure, as $\log P^o$/ppm at 25 °C

VOC	$\log P^o$	VOC	$\log P^o$
Oct-1-yne	4.23	*s*-Butanol	4.34
Propanone	5.48	*t*-Butanol	4.73
Pentan-2-one	4.67	Pentan-1-ol	3.40
Heptan-2-one	3.70	Hexan-1-ol	2.94
Nonan-2-one	2.73	Heptan-1-ol	2.37
Methyl acetate	5.45	Heptan-4-ol	3.10
Ethyl acetate	5.10	Octan-1-ol	2.00
Propyl acetate	4.65	Toluene	4.57
Butyl acetate	4.18	Ethylbenzene	4.10
s-Butyl acetate	4.49	Propylbenzene	3.65
t-Butyl acetate	4.70	Chlorobenzene	4.20
Pentyl acetate	3.73	Pyridine	4.43
Hexyl acetate	3.26	Butanal	5.16
Heptyl acetate	2.81	Pentanal	4.75
Octyl acetate	2.38	Hexanal	4.28
Decyl acetate	1.48	Heptanal	3.81
Dodecyl acetate	0.49	Octanal	3.50
Methanol	5.22	Formic acid	4.75
Ethanol	4.89	Butanoic acid	3.02
Propan-1-ol	4.43	Hexanoic acid	1.82
Propan-2-ol	4.75	Octanoic acid	0.81
Butan-1-ol	3.92	Acetic acid	4.31

A plot of Eq. 6 is shown in Fig. 2 from which it can be seen that not only acetic acid (not included in the regression equation) but also formic acid is an outlier. In principle, Eq. 6 could be used to obtain rough estimates of NPT values. In practice, it is easier to obtain the compound descriptors used in Eq. 5 than it is to determine vapour pressure; thus Eq. 6 has no advantage over Eq. 5 as regards estimation of nasal pungency thresholds. The success of the general LFER, or QSAR, Eq. 1 in correlating the log(1/NPT) values in Table 2, has a number of implications. Firstly, Eq. 1 has been set up to analyse transport related processes, that is processes in which the main factor is the transfer or transport of a compound from one phase to another. It has not been set up to deal with processes such as drug-receptor interactions, and indeed cannot do so. We must therefore deduce that in nasal pungency, a major process is simply the transfer of a VOC from the air stream to a receptor area. If this is so, then the coefficients in Eqs. 4 or 5 will reflect the chemical properties of the receptor area, as we have suggested above.

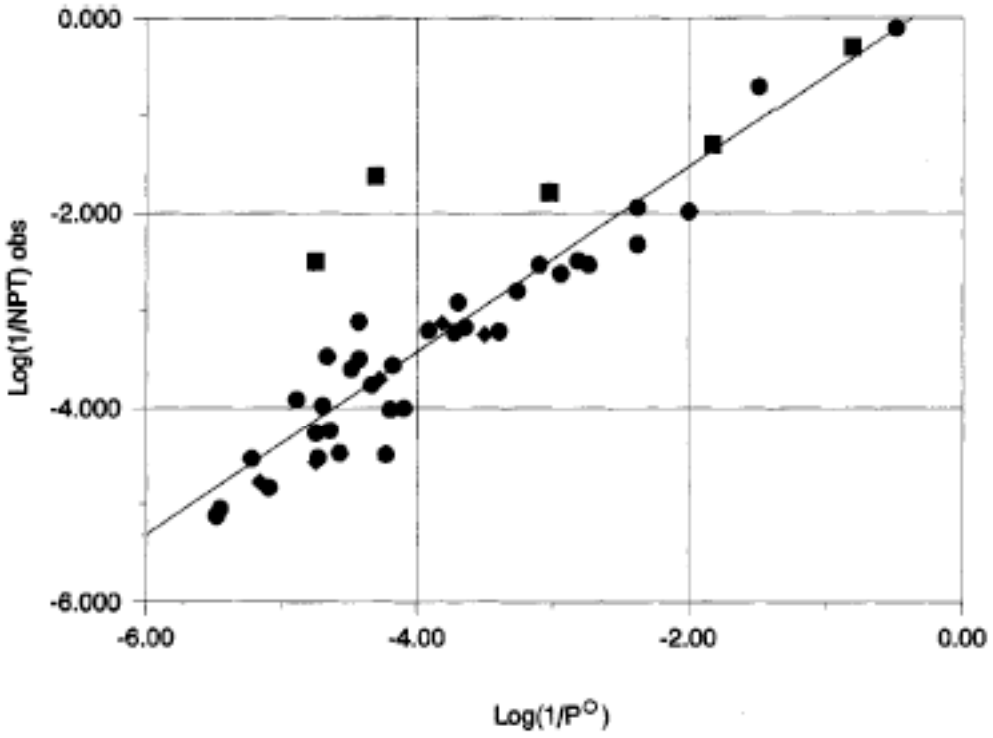

Fig. 2 Plot of log(1/NPT) observed vs log(1/P°). Symbols are as for Fig. 1; note the outlying points for formic acid and acetic acid

From Table 1 we can deduce that the main transfer does not take place from the gas phase to an aqueous environment: compare the coefficients for log(1/NPT) with those for transfer from the gas phase to water. The receptor area is just as basic (in the hydrogen bond sense) as water, but is very much less acidic. The tertiary amide N-formylmorpholine is a reasonable model for the receptor area, except that this amide lacks any hydrogen-bond acidity. Possibly a secondary or primary amide might be a good model for the receptor area.

Predictions of NPTs

We consider the use of the algorithm, Eq. 5, in the prediction of further values of nasal pungency thresholds. The NPT values used here tend to be higher than those reported in a review by Ruth (see for example, Ruth 1986). A recent paper (Cometto-Muñiz and Cain 1997) discusses the factors affecting the measurements of sensory irritation thresholds, including subjects, comparison of modalities, and methods of measurement. However, judging from the generality of the key Eq. 1, we can expect Eq. 5 to apply to other members of the various functional series in Table 2, and also to other functional series altogether. These might include aliphatic VOCs such as alkanes, cycloalkanes, alkenes, ethers, amides and halogenated compounds, and aromatic VOCs such as ethers, halocompounds, aldehydes, ketones, esters, amides and alcohols. There are two possible caveats. Firstly, the VOCs must be those regarded as nonreactive, so that allyl compounds, aliphatic amines, benzyl halides, etc., must be excluded (Alarie et al. 1997)

until such time as are shown to be unreactive as regards NPT values towards man upon brief (1±3 s) presentations. For reactive compounds, Eq. 5 will predict a minimum potency which will invariably be less than the observed potency. Secondly, care should be taken not to extrapolate too far along homologous series in view of possible cut-off effects. It is already known (Cometto-Muñiz et al. 1997) that a number of higher homologues sometimes fail to evoke pungency. These VOCs include octan-1-ol, octyl- and higher acetates, propyl- and higher alkylbenzenes, hexanoic acid, octanoic acid and octanal. For the aliphatic acetates and aldehydes, this failure to evoke pungency is probably not due to a physical cut-off mechanism but may be due to a biological cut-off related to molecular size (Cometto-Muñiz et al. 1997). For the other series there are not enough data to suggest reasons for the cut-off effect. Molecules of nonane, nonene, octanal, octan-2-one, and dibutylether have about the same length in an extended conformation; thus it is probably safe to use Eq. 5 to predict NPT values for homologues up to these molecules. If higher homologues do exhibit cut-off effects, then the predicted irritation potency via Eq. 5 will always be greater than observed, i.e. the predicted NPT values will be lower than those observed.

Even with these precautions, we are now in a position to predict NPT values in man for hundreds of further VOCs for which we have the necessary descriptors in Eq. 5. Already descriptors for over 400 VOCs have been published (Abraham 1993; Abraham et al. 1994a), and prediction of NPT values for the nonreactive VOCs in this set is therefore trivial. At present, we are determining descriptors for specific series of VOCs, including terpenes, in order to extend predictions to other VOCs in indoor air.

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