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## **The Correlation and Prediction of VOC Thresholds for Nasal Pungency, Eye Irritation and Odor in Humans**

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### **Abstract**

A general equation set up for the study of transport properties has been applied to VOC nasal pungency and eye irritation thresholds, as  $\log(1/NPT)$  and  $\log(1/EIT)$ . The equation accounts for 93-95 % of the total effect, thus suggesting that the main step is transport of the VOC from the gas phase to a receptor phase. In the case of odor thresholds, ODT, the general equation accounts for only 77% of the total effect. A modified equation incorporates a factor for aliphatic aldehydes and carboxylic acids, and a general size effect that depends on the VOC maximum length. The size effect is important in that it leads to a cut-off effect that greatly reduces the potency of higher homologues. The various equations can all be used to predict chemosensory thresholds for thousands of VOCs.

**Keywords:** VOCs, chemosensory thresholds, cut-off, potency

## **Introduction**

The presence of volatile organic compounds (VOCs) in the environment can lead to widely-cited health effects, such as sensory irritation [1,2]. Indeed, about half the threshold limit values (TLVs) set by the American Conference of Governmental Industrial Hygienists is based on sensory irritation [3]. Over the past ten years, we have carried out a systematic investigation into thresholds for sensory irritation (nasal pungency and eye irritation) and odor, using panels of human subjects under carefully controlled conditions [4-10]. Of course, in order to obtain thresholds for nasal pungency we have had to study anosmics – persons with no sense of smell. As a result of our efforts, we now have a data base of some 50 VOCs for which we have chemosensory thresholds. However, the number of VOCs that can be encountered at home or in the work place is orders of magnitude larger. There are more than 100,000 industrial chemicals, and even if only a third could be classed as VOCs or semi-volatile organic compounds, it is obvious that experimental determination of potency towards humans cannot possibly be extended to more than a very small proportion. The use of animal experiments does allow the study of VOCs that are too toxic to be tested on humans, but does not help very much as regards the sheer number of compounds examined. The comprehensive survey of Schaper [11] on upper respiratory tract irritation in mice includes data on only 244 VOCs.

There is therefore a very definite need for some type of prediction of the potency of VOCs towards humans. Even if restricted to VOCs that act through ‘physical’ mechanisms, rather than through ‘chemical’ or ‘reactive’ mechanisms, such predictions would considerably help to fill the gap between the relatively small number of VOCs studied to date, and the very large number of chemicals that could potentially be encountered.

It is the aim of this paper to set out the methods we have used to correlate chemosensory thresholds, by means of quite simple algorithms that can be used for the prediction of a very large number of additional thresholds.

## **Methods**

Our general approach is to regard the phenomena of sensory irritation and odor as mainly physical processes in which a VOC is transported to a receptor or receptor area. We realise that this will be an approximation only, especially in the case of odor thresholds, and we stress at the outset that any analysis of odor thresholds will not be the same as the numerous analyses of odor quality that have been carried out [12, 13]. As a starting point for our analysis of sensory irritation, we can take the suggestion previously put forward to explain the effect of VOCs on upper respiratory tract irritation in mice [14]. It was postulated that a physicochemical equilibrium was set up between a VOC in the initial gas phase and a VOC at a receptor or receptor area. Once at, or adjacent to, the receptor, a VOC simply activates the receptor by an ‘on-off’ mechanism, so that the entire (or main) effect of a VOC takes place through the physicochemical equilibrium. We can therefore reduce the problem to that of the study of such an equilibrium, or partition, between the gas phase and some medium into which the VOC is transported. As we shall see, this simple treatment will not suffice for odor thresholds, and so we shall deal first with sensory irritation, and then examine what other effects are needed to account for odor thresholds.

If the main process in sensory irritation is an equilibrium or partition between a VOC in the gas phase and in the receptor medium, we require a methodology that is already known to account for similar equilibria. We have, indeed, constructed a rather simple equation [15,16] that has already been applied to the partition of

compounds between the gas phase and water, alcohols and other solvents [17-20] and a number of biological phases [21] as well as to numerous sets of gas chromatographic data [22].

$$\log SP = c + eE + sS + aA + bB + lL \quad (1)$$

In equation (1), the dependent variable,  $\log SP$ , is some property of a series of VOCs in a given system. The independent variables in equation (1) are [16] properties or descriptors of the VOCs, as follows: **E** is an excess molar refraction, **S** is the dipolarity/polarizability, **A** and **B** are the overall or effective hydrogen-bond acidity and basicity, and **L** ( $\log L^{16}$ ) is defined through  $L^{16}$ , the solute Ostwald solubility coefficient on hexadecane at 298K. The **L**-descriptor is itself a combination of two solute properties, (i) a general measures of solute size and (ii) the ability of a solute to interact with a solvent phase through dispersion forces. The units of **E** are  $\text{cm}^3/10$ ; the other descriptors have no units because they are all derived from the logarithm of equilibrium constant. The coefficients  $c$ ,  $e$ ,  $s$ ,  $a$ ,  $b$  and  $l$  are found by multiple linear regression analysis. They reflect the complementary properties of the receptor phase. The  $e$ -coefficient gives the tendency of the phase to interact with VOCs through polarizability-type interactions, mostly via electron pairs. The  $s$ -coefficient is a measure of the phase dipolarity/polarizability. The  $a$ -coefficient represents the complementary property to VOC hydrogen-bond acidity and so is a measure of the phase hydrogen-bond basicity. Likewise, the  $b$ -coefficient is a measure of the phase hydrogen-bond acidity. Finally, the  $l$ -coefficient is a measure of the hydrophobicity of the phase.

In order to apply equation (1) to any given process, a reasonable number of data

points of the property to be correlated are needed as the dependent variable. Simple multiple linear regression against the known VOC descriptors leads to the coefficients. Once the latter have been calculated, then for any other VOC for which the descriptors are available, the property can trivially be calculated.

## Results

**Sensory irritation thresholds** - We have previously used equation (1) to correlate nasal pungency thresholds (NPT, in ppm) for 43 varied compounds [23], leading to equation (2),

$$\log (1/\text{NPT}) = -8.519 + 2.154 \mathbf{S} + 3.522 \mathbf{A} + 1.397 \mathbf{B} + 0.860 \mathbf{L} \quad (2)$$

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

Here and elsewhere,  $n$  is the number of data points (i.e. the number of VOCs),  $r$  is the correlation coefficient,  $\text{SD}$  is the standard deviation in the dependent variable, and  $F$  is the F-statistic. The  $e$ -coefficient of the independent variable,  $\mathbf{E}$ , was statistically not significant. The reciprocal of NPT values was used, so that the more potent the VOC the larger is the value of  $\log (1/\text{NPT})$ .

The coefficients in equation (2) can be compared to those for various gas-condensed phase partitions that take place by simple transfer mechanisms, as shown in Table 1 [17-20]. There is much similarity between the NPT equation and equations for the solubility of gaseous VOCs in solvents such as wet octan-1-ol and methanol. There is also some similarity with equations for the solubility of gaseous VOCs in a number of biophases [21]. Thus equation (2) can be regarded as an equation for simple transfer of VOCs from the gas phase to a biophase. It is interesting that

equation (2) includes a wide variety of VOCs, including carboxylic acids, aldehydes, ketones, alcohols, etc., with only one outlier - acetic acid.

Subsequent to the construction of equation (2), we determined descriptors for a number of terpenes [10], and so were then able [24] to test the predictive power of equation (2), as shown in Table 2. Bearing in mind that the error in the observed log NPT values is about 0.22, and that in the predicted values is about 0.27, the agreement is reasonably good. We can update the NPT equation by incorporation of the data for the terpenes to give equation (3),

$$\log (1/\text{NPT}) = -8.080 + 1.767 \mathbf{S} + 3.298 \mathbf{A} + 1.076 \mathbf{B} + 0.857 \mathbf{L} \quad (3)$$

$$n = 48, r^2 = 0.950, \text{SD} = 0.27, F = 211$$

Since equation (3) covers a very wide spread of log (1/NPT) values, from -0.10 to -5.12, and a wide range of types of VOC, it represents a simple way of predicting values of NPT for a very large number of VOCs.

In the case of eye irritation thresholds (EIT), not enough VOCs had been studied to construct a similar equation. However, we showed [25] that scores for the Draize rabbit eye irritation test for VOCs administered as the pure liquids [26] could be transformed into equivalent EIT values through equation (4),

$$\text{Log} (\text{DES}/P^{\circ}) - 0.63 = \log (1/\text{EIT}) \quad (4)$$

In equation (4), DES is the Draize score;  $P^{\circ}$  is the saturated vapor pressure of the liquid VOC in ppm at 298K, and serves to correct the DES scores from the state of

pure liquid to the gaseous state. The constant 0.63 is purely empirical and simply connects the DES and EIT scales. We then had a total of 54 EIT values, of which 17 we had directly measured on human subjects, and 37 of which were obtained via equation (4). Application of equation (1) to the EIT values, as  $\log(1/\text{EIT})$ , then yielded [25] equation (5),

$$\log(1/\text{EIT}) = -7.918 - 0.482 \mathbf{E} + 1.420 \mathbf{S} + 4.025 \mathbf{A} + 1.219 \mathbf{B} + 0.853 \mathbf{L} \quad (5)$$

$$n = 54, r^2 = 0.928, \text{SD} = 0.36, F = 124$$

Just as for the NPT equation, equation (5) covers a wide enough spread of  $\log(1/\text{EIT})$  values (from 0.20 to  $-5.46$ ) and type of VOC to be useful as general predictive equation. Comparison of coefficients of equation (5) with those for gas-solvent phase transport properties shows that equation (5) is very comparable to simple transport equations for partition from the gas phase to organic solvents or to biological phases, see Table 1. Thus for both sensory effects, the transport step must be the main process involved. However, we know that there are limitations to equations (3) and (5). In particular, we have recently observed that the potency of higher homologues in a series becomes less than predicted, and we attribute this to a ‘cut-off’ effect. The cut-off is not just a manifestation of the very low saturated vapor pressure of the higher homologues, but seems to be a chemical cut-off that is related to the actual mechanism of irritation. At the moment, we are working on modifications of equations (3) and (5) that will incorporate a method of calculating this cut-off effect.

**Odor thresholds** - There have been a number of early correlations of odor thresholds with various properties of odorants [27-30] but none have been very good statistically, and none have led to any conclusions of mechanistic significance. Two later studies



related ODT values to properties of homologous series of odorants. A study of ODT values [31] showed that for several homologous series, the ODT values could be correlated with the odorant activity coefficient in water [32]. Such correlations are of limited practical use, and of no mechanistic value. A more detailed analysis [33,34] led to equation (6), where the ODT values were taken from the AIHA compilation [35].

$$\log [\{\text{ODT}\}K^{\text{W}}] = a - b \log P(\text{oct}) \quad (6)$$

Here  $K^{\text{W}}$  is the air-water partition coefficient, also known as the Ostwald solubility coefficient, and  $P(\text{oct})$  is the water-octanol partition coefficient; the coefficients  $a$  and  $b$  vary from one homologous series to another. Rearrangement of equation (6) leads to equation (7),

$$\log [1/\text{ODT}] = -a + \log K^{\text{W}} + b \log P(\text{oct}) \quad (7)$$

Now when  $b$  is close to unity,  $[\log K^{\text{W}} + \log P(\text{oct})] = \log K^{\text{OCT}}$ , where  $K^{\text{OCT}}$  is the partition coefficient between the gas phase and octanol (or, rather, wet octanol). For a number of homologous series,  $b$  ranged between 0.91 and 1.88 [34]. Hence the mechanistic significance of equation (6) is that the main process is transfer of the VOC from the gas phase to a medium that resembles wet octanol.

It seems rather clear, however, that odor thresholds do not just reflect a simple transfer from the gas phase to a receptor area. Once in the airspace above the olfactory mucosa, the molecules must diffuse through a layer of mucus (10-30 microns thick) to

gain access to the receptors themselves [36, 37]. Such diffusion, or transport, may involve (at least in part) odorant binding proteins (OBPs) that can act as carriers [38-41]. Once transported across the mucosal layer to a receptor area or biophase, the VOC (or the VOC/OBP complex) can then interact with odor receptors at the surface of the cilia membrane of the olfactory neuron. Our procedure is to apply the general equation (1) to ODT values, in the hope that we might deduce whether or not the resulting equation is consistent with simple transfer of VOCs from the gas phase to a biophase.

We applied equation (1) to all the VOCs for which we had data except the carboxylic acids and aliphatic aldehydes that were clearly out-of-line [42]. The VOCs, propanone, octan-1-ol, methyl acetate and t-butyl acetate were then also revealed to be outliers, and were removed to yield the correlation equation,

$$\text{Log (1/ODT)} = -5.154 + 0.533 \mathbf{E} + 1.912 \mathbf{S} + 1.276 \mathbf{A} + 1.559 \mathbf{B} + 0.699 \mathbf{L} \quad (8)$$

$$n = 50, r^2 = 0.773, \text{SD} = 0.579, F = 28.7$$

The coefficients in equation (8) are very similar to those for transfer from the gas phase to organic solvents, see Table 1. It therefore appears that simple transfer from the gas phase to a biophase must play a major role in the relationship of odor thresholds to the structure of VOCs, of the order of 77% of the total effect. This contrasts with the corresponding equations for  $\log (1/\text{NPT})$  and  $\log (1/\text{EIT})$  that account for 93-95% of the total effect.

Examination of equation (8) showed that both small VOCs and large VOCs are less potent than expected. We then calculated the maximum length, **D**, of the VOC through a computer-assisted molecular-modelling program [43], and found that a

parabolic term, ( $\mathbf{D} - \mathbf{D}^2$ ), could account for the lack of potency of both small and large VOCs, as in equation (9).

$$\log (1/\text{ODT}) = -6.757 + 0.533\mathbf{E} + 1.912 \mathbf{S} + 1.276 \mathbf{A} + 1.559 \mathbf{B} + 0.699 \mathbf{L} \\ + 0.297 \mathbf{D} - 0.013 \mathbf{D}^2 \quad (9)$$

$$n = 50, r^2 = 0.82, \text{SD} = 0.511$$

We can include the carboxylic acids and aliphatic aldehydes into the regression equation by means of an indicator variable,  $\mathbf{H}$ , chosen as 2.0 for the carboxylic acids and aldehydes and zero for all other VOCs,

$$\log (1/\text{ODT}) = -7.445 + 0.304\mathbf{E} + 1.652 \mathbf{S} + 2.104 \mathbf{A} + 1.500 \mathbf{B} + 0.822 \mathbf{L} \\ + 0.369 \mathbf{D} - 0.016 \mathbf{D}^2 + 1.000 \mathbf{H} \quad (10)$$

$$n = 60, r^2 = 0.84, \text{SD} = 0.601$$

Equation (10) is a general equation for  $\log (1/\text{ODT})$  values, and could be used to predict further values to about 0.6 log units, of the order of experimental error. Four compounds are again outliers, viz. propanone, methyl acetate, t-butyl acetate and octan-1-ol, but we suspect increased experimental error in the case of the first three.

The necessity for the use of an indicator variable for aldehydes and carboxylic acids arises because these two sets of compounds are more potent than predicted by equation (9). There is precedent for the extra potency of aldehydes and carboxylic acids, as found [44] for sensory irritation in mice.

According to equations (8-10), a large part of the variation in  $\log (1/\text{ODT})$  values

with the structure of the VOCs is due to simple transport of the VOC from the gas phase to a biophase, that is discrimination amongst VOCs is selective but is not very specific [42]. In addition, there is an effect that we suggest is due to the size of the VOC, as measured by the maximum length. One possible mechanism includes simple transfer from the gas phase to a biophase mediated by transport by OBPs. We have obtained some information as to the role of OBPs from recent work [41] in which complexation constants for a number of VOCs with porcine OBP were measured. However, we showed [42] that over the range of VOCs studied, the complexation constant, as  $\log(1/C)$  varied by 0.75 log units, whereas  $\log(1/ODT)$  varied by no less than 3.99 log units. It is therefore possible that the effect of OBPs is not the prime reason for the variation of  $\log(1/ODT)$ , but that complexation to OBPs (or possibly the rate of complexation to OBPs) mediates the effect of transport to, and interactions with, the receptor phase.

Equation (10) has considerable consequences, especially for the effect of homologues. On equation (10), values of  $\log(1/ODT)$  along an homologous series do not increase regularly, but gradually become smaller than expected from a linear relationship and eventually even begin to decrease. This corresponds to a chemical cut-off in potency, a prediction that is completely outside the scope of previous analyses [32-33]. This predicted cut-off effect has a very important consequence. Hau *et al.* [34] have used their partition model [33] to predict odor thresholds for VOCs found in the indoor environment. This partition model does not include any cut-off effect at all, and hence higher homologues will be predicted to be much more potent than on our model.

The odor perception of enantiomers is well known, but invariably in terms of odor quality. Rossiter [12] and Laska *et al.* [45] list pairs of enantiomers that elicit different

sensations of odor quality. The latter workers tested odor discrimination of 10 pairs of enantiomers and concluded that within their experimental procedure, differences in odor intensity played little or no part in discrimination of the two enantiomeric forms. Other workers have shown that ODTs for *R*(+)- and *S*(-)-nicotine are essentially the same [46]. This suggests selective, rather than specific, transport of VOCs to the biophase, and is in accord with our model.

## **Conclusions**

Simple transport-based equations have been constructed for NPT and EIT values. These equations can be used to predict further NPT and EIT values for VOCs for which we have the required descriptors, **E**, **S**, **A**, **B** and **L**. The more complicated equation for ODT values also requires a calculation of the maximum length of a VOC, but the calculation can be carried out relatively easily [43]. In Table 3 are given the number of compounds for which we have descriptors. The minimum number of compounds is 2580 for **L**, most of these being VOCs or semi-volatile organic compounds. We can therefore trivially calculate the three sets of chemosensory thresholds for over 2500 compounds. As an example, we have recently determined descriptors for a number of refrigerants, and have predicted their nasal pungency thresholds [47].

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## References

- [1] Cometto-Muñiz JE, Cain WS: Sensory irritation: relation to indoor air pollution *Ann N Y Acad Sci* 1992; 641: 137-151.
- [2] Mølhave, L Controlled experiments for studies of the sick building syndrome *Ann New York Acad Sci* 1992; 641: 46-55.
- [3] American Conference of Governmental Industrial Hygienists, ACGIH, *Threshold limit values for chemical substances and physical agents, and biological exposure indices*. ACGIH, Cincinnati. 1991-1992.
- [4] Cometto-Muñiz JE, Cain WS: Thresholds for odor and nasal pungency *Physiol. Behav* 1990; 48:, 719-725
- [5] Cometto-Muñiz JE, Cain WS: Nasal pungency, odor and eye irritation thresholds for homologous acetates *Pharmacol. Biochem. Behav.* 1991 39, 983-989
- [6] Cometto-Muñiz JE, Cain WS: Efficacy of volatile organic compounds in evoking nasal pungency and odor *Arch Environ Health* 1993; 48: 309-314
- [7] Cometto-Muñiz JE, Cain WS: Sensory reactions of nasal pungency and odor to volatile organic compounds-the alkylbenzenes *Am Ind Hyg Ass J* 1994: 55; 811-817
- [8] Cometto-Muñiz JE, Cain WS: Relative sensitivity of the ocular trigeminal, nasal trigeminal, and olfactory systems to airborne chemicals *Chem Senses* 1995; 20: 191-198
- [9] Cometto-Muñiz JE, Cain WS, Abraham MH: Nasal pungency and odor of homologous aldehydes and carboxylic acids *Exp Brain Res* 1998; 118: 180-188.
- [10] Cometto-Muñiz JE, Cain WS, Abraham MH, Kumarsingh R: Trigeminal and olfactory chemosensory impact of selected terpenes *Pharmacol Biochem Behav* 1998; 60: 765-779.
- [11] Schaper M, Development of a data base for sensory irritants and its use in establishing occupational exposure limits. *Am Ind Hyg Assoc J* 1993; 54: 488-544.
- [12] Rossiter KJ: Structure-odor relationships. *Chem Rev* 1996; 96:, 3201-3240.
- [13] Pybus DH, Sell CS: *The chemistry of fragrances*. Royal Society of Chemistry,

London. 1999.

- [14] Abraham MH, Nielsen GD, Alarie Y: The Ferguson principle and an analysis of biological activity of gases and vapors J Pharm Sci 1994; 83: 680-688.
- [15] Abraham MH, Whiting GS, Doherty RM, Shuely WJ: Hydrogen bonding. 16. A new solute solvation parameter,  $\pi_2^H$ , from gas chromatographic data J Chromatogr 1991; 587: 213-228.
- [16] Abraham MH: Scales of solute hydrogen-bonding: their construction and application to physicochemical and biochemical processes Chem Soc Revs 1993; 22: 73-83.
- [17] Abraham MH, Andonian-Haftvan J, Whiting GS, Leo A, Taft RW: Hydrogen bonding. Part 34. The factors that influence the solubility of gases and vapours in water at 298 K, and a new method for its determination J Chem Soc Perkin Trans2 1994: 1777-1791.
- [18] Abraham MH, Whiting GS, Carr PW, Ouyang H: Hydrogen bonding. Part 45. The solubility of gases and vapours in methanol at 298K: an LFER analysis, J Chem Soc Perkin Trans 2 1998: 1385-1390.
- [19] Abraham MH, Platts JA, Hersey A, Leo AJ, Taft RW: Correlation and estimation of gas-chloroform and water-chloroform partition coefficients by linear free energy relationship method: J Pharm Sci 1999; 88: 670-679.
- [20] Abraham MH, Le J, Acree WE Jr : The solvation properties of the aliphatic alcohols: Collect Czech Chem Comm 1999; 64: 1748-1760
- [21] Abraham MH, Weathersby PK: Hydrogen bonding. 30. Solubility of gases and vapors in biological liquids and tissues J Pharm Sci 1994; 83: 1450-1456.
- [22] Abraham MH, Poole CF, Poole SK: Classification of stationary phases and other materials by gas chromatography J Chromatogr A 1999; 842: 79-114.
- [23] Abraham MH, Kumarsingh R, Cometto-Muñiz JE, Cain WS: An algorithm for nasal pungency thresholds in man Arch Toxicol 1998; 72: 227-232.
- [24] Abraham MH, Kumarsingh R, Cometto-Muñiz JE, Cain WS, Roses M, Bosch E, Diaz ML: The determination of solvation descriptors for terpenes, and the prediction of nasal pungency thresholds J Chem Soc Perkin Trans 2 1998 2405-2411.
- [25] Abraham MH, Kumarsingh R, Cometto-Muñiz JE, Cain WS: Draize eye scores and eye irritation thresholds in man combined into one quantitative

- structure-activity relationship *Toxicol In Vitro* 1998; 12: 403-408.
- [26] Cronin MTD, Basketter DA, York M: A quantitative structure-activity relationship (QSAR) investigation of a Draize eye irritation database. *Toxicol In Vitro* 1994; 8: 21-28
- [27] Dravnieks A: A building block model for the characterization of odorant molecules and their odors *Ann New York Acad Sci* 1974; 237: 144-163.
- [28] Laffort P, Patte F: Solubility factors established by gas-liquid chromatography *J Chromatogr* 1987; 406: 51-74.
- [29] Chastrette M: Trends in structure-odor relationship. SAR and QSAR in *Environmental Res* 1997; 6: 215-254.
- [30] Chastrette M, Thomas-Danguin T, Rallett E: Modelling the human olfactory stimulus-response function *Chem Senses* 1998; 23: 181-196.
- [31] Devos M, Patte F, Roualt J, Laffort P, Van Gemert LJ: Standardized human olfactory thresholds, IRL Press, Oxford, 1990.
- [32] Yamanaka T: (1995) Contribution of activity coefficients of methylene homologues to odor and flavor detection thresholds *Chem Senses* 1995; 29: 471-475
- [33] Hau KM, Connell DW: Quantitative structure-activity relationships (QSARs) for odor thresholds of volatile organic compounds (VOCs) *Indoor Air* 1998; 8: 23-33.
- [34] Hau KM, Connell DW, Richardson BJ Use of partition models in setting Health guidelines for volatile organic compounds *Regulatory Toxicology and Pharmacology* 2000; 31: 22-29
- [35] AIHA Odor thresholds for chemicals with established occupational health standards. Ohio, American Industrial Hygiene Association, 1989.
- [36] Hornung DE, Mozell MM: Accessibility of odorant molecules to the receptors. In Cagan, R.H and Kare, M.R (eds), *Biochemistry of taste and olfaction*, New York, London Academic Press 1981; 33-45.
- [37] Snyder SH, Sklar PB, Pevsner J: Molecular mechanism of olfaction *J Biolog Chem* 1988; 263: 13971-13974
- [38] Bianchet MA, Bains G, Pelosi P, Pevsner J, Snyder SH, Monaco HL, Amzel LM: The three-dimensional structure of bovine odorant binding protein and its mechanism of odor recognition *Nature Struct Biol* 1996; 3: 934-939.



- [39] Brownlow S, Sawyer L: Waiting to inhale *Nature Struct Biol* 1996; 3: 902-906.
- [40] Tegoni M, Ramoni R, Bignetti E, Spinelli S, Cambillau C: Domain swapping creates a third putative combining site in bovine odorant binding protein dimer *Nature Struct Biol* 1996; 3: 863-867.
- [41] Vincent F, Spinelli S, Raamolni R, Pelosi P, Cambillo C, Tegoni M: Complexes of porcine odorant binding proteins with odorant molecules belonging to different chemical classes *J.Mol.Biology* 2000; 300: 127-139.
- [42] Abraham MH, Gola JMR, Cometto-Muñiz JE, Cain WS: A model for odor thresholds submitted.
- [43] Molecular Modeling Pro (TM) Revision 3.1 ChemSW software Inc: 1992.
- [44] Alarie Y, Schaper M, Nielsen GD, Abraham MH: Structure-activity relationships of volatile organic chemicals as sensory irritants *ArchToxicol* 1998; 72: 125-140.
- [45] Laska M, Liesen A, Teubner P: Enantioselectivity of odor perception in squirrel monkeys and humans *Am J Physiol* 1999; 277 (Regulatory Integrative Comp Physiol 46) R1098-R1103.
- [46] Thuerauf N, Kaegler M, Dietz R, Barocka A, Kobal G: Dose-dependent stereoselective activation of the trigeminal sensory system by nicotine in man *Psychopharmacol* 1999; 142: 236-243.
- [47] Abraham MH, Gola JMR, Cometto-Muñiz JE, Cain WS: Solvation properties of refrigerants, and the estimation of their water-solvent and gas-solvent partitions *Fluid Phase Equilibria* 2001; 180: 41-58.

**Table 1.** Regression coefficients in equation (1) for gas-solvent (phase) partitions at 298K

Phase	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>
Wet octan-1-ol	0.002	0.709	3.519	1.429	0.858
Dry methanol	-0.215	1.173	3.701	1.432	0.769
Dry ethanol	-0.206	0.789	3.635	1.311	0.853
Dry octan-1-ol	-0.204	0.564	3.582	0.694	0.939
Chloroform	-0.467	1.203	0.138	1.432	0.994
Acetone	-0.277	1.522	3.258	0.078	0.863
Dimethylformamide	-0.189	2.327	4.756	0.000	0.808
Water	0.822	2.743	3.904	4.814	-0.213
Brain <sup>a</sup>	0.427	0.286	2.781	2.787	0.609
Muscle <sup>a</sup>	0.544	0.216	3.471	2.924	0.578
Fat <sup>a</sup>	-0.172	0.729	1.747	0.219	0.895
NPT, equation (2) <sup>a</sup>	0.000	2.154	3.522	1.397	0.860
EIT, equation (5) <sup>a</sup>	-0.482	1.420	4.025	1.219	0.853
ODT, equation (8) <sup>a</sup>	0.533	1.912	1.276	1.559	0.699

<sup>a</sup> At 310 K

**Table 2.** Observed and predicted values of log NPT for terpenes, on equation (2)

Terpene	Obs	Pred
Menthol	1.71	1.37
1,8-Cineole	2.37	2.71
Linalool	2.55	1.57
<i>p</i> -Cymene	3.05	3.25
$\Delta$ -3-Carene	3.21	3.91
$\alpha$ -Terpinene	3.30	3.71

**Table 3.** Number of compounds for which descriptors are available.

<b>E</b>	4170
<b>S</b>	3640
<b>A</b>	4380
<b>B</b>	3320
<b>L</b>	2580

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