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A Quantitative Structure-Activity Analysis on the Relative Sensitivity of the Olfactory and the Nasal Trigeminal Chemosensory Systems

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Running head: Relative Sensitivity of Olfaction and Nasal Chemesthesis

Abstract

We have applied a quantitative structure-activity (QSAR) approach to analyse the chemical parameters that determine the relative sensitivity of olfaction and nasal chemesthesis to a common set of volatile organic compounds (VOCs). We used previously reported data on odor detection thresholds (ODTs) and nasal pungency thresholds (NPTs) from 64 VOCs belonging to seven chemical series (acetate esters, carboxylic acids, alcohols, aliphatic aldehydes, alkylbenzenes, ketones, and terpenes). The analysis tested whether NPTs could be used to separate out "selective" chemosensory effects (i.e., those resting on the transfer of VOCs from the gas phase to the receptor phase) from "specific" chemosensory effects in ODTs. Previous work showed that selective effects overwhelmingly dominate chemesthetic potency whereas both selective and specific effects control olfactory potency. We conclude that it is indeed possible to use NPTs to separate out selective from specific effects in ODTs. Among the series studied, aldehydes and acids, except for formic acid, show clear specific effects in their olfactory potency. Furthermore, for VOCs whose odor potency rests mainly on selective effects, we have developed a QSAR equation that can predict their ODTs based on their NPTs.

Key words: VOCs, olfactory QSAR, chemesthetic QSAR, odor detection thresholds, nasal irritation thresholds, nasal chemosensory sensitivity, mechanism of biological activity

Introduction

Humans rely principally on two chemosensory systems to detect airborne chemicals: Olfaction and chemesthesis. The sense of smell is restricted to the nasal cavity and mediated by the olfactory nerve. In contrast, chemesthesis (Bryant and Silver, 2000), or chemical feel, is present in all mucosae, also in the skin under the epidermis (Keele, 1962), and is mediated by a variety of nerves, depending on the location of stimulation. Due to their direct exposure to the air we breathe and that surrounds us, the nasal and the ocular mucosa are common sites of chemesthetic stimulation (Doty et al., 2004). Nasal chemesthesis includes sensations such as stinging, freshness, prickling, piquancy, tingling, irritation, burning and the like, which, due to their sharp nature, we group together under the term nasal pungency. Chemesthesis in both sites is mediated by the trigeminal nerve, see review in (Doty and Cometto-Muñiz, 2003). In the present paper we will focus on the comparative sensitivity of olfaction and nasal chemesthesis towards volatile organic compounds (VOCs), using a quantitative structure-activity relationship (QSAR) approach.

Odorants reaching the lumen above the olfactory epithelium transfer from the gas phase into the mucus phase and they continue to be distributed among the various biophases until they reach the olfactory receptors (ORs) (Rawson and Yee, 2006) in the membrane of the cilia of olfactory sensory neurons (OSNs) (Flannery et al., 2006; Schwarzenbacher et al., 2005). ORs belong to the large family of G-protein coupled receptors (GPCRs) (Breer, 2003; Liman, 2006). In humans there are about 388 genes coding for functional ORs and about 414 pseudogenes that do not code for functional ORs (Niimura and Nei, 2006). Each odorant is believed to activate a specific pattern of ORs (Malnic et al., 1999).

Irritants entering the nasal cavity also transfer from the gas phase into the mucus and other biophases until they reach chemesthetic receptors in free nerve endings of the trigeminal nerve (Finger et al., 1990), particularly from C and A_{delta} fibers. Trigeminal chemoreceptors include vanilloid (Silver et al., 2006; Tominaga and Tominaga, 2005), nicotinic acetylcholine (Alimohammadi and Silver, 2000; Thuerauf et al., 1999; Thuerauf et al., 2006), and menthol (Damann et al., 2006; Kobayashi et al., 2005) receptors.

Capsaicin, menthol, and a variety of pungent compounds stimulate sensory nerve fibers via activation of members of a family of transient receptor potential (TRP) channels (Jordt et al., 2004; Macpherson et al., 2005; Macpherson et al., 2006; Trevisani et al., 2002) that includes about 30 members (Montell, 2005; Ramsey et al., 2006). These and other receptors and mechanisms (Inoue and Bryant, 2005), including cell damage by reactive VOCs and consequent release of nociception mediators (Sutherland et al., 2000), could play a role in nasal chemesthesis as evoked by common VOCs, including alcohols, esters, ketones, alkylbenzenes, aldehydes, etc. (Cometto-Muñiz, 2001).

In the main, VOCs that can evoke irritation can also evoke odor. A previous separate QSAR analysis on nasal pungency thresholds (NPTs) (Abraham et al., 1998) and odor detection thresholds (ODTs) (Abraham et al., 2002) revealed that "selective" processes (e.g., transfer driven effects in which small structural changes in the VOC evoke predictable, and rather small, changes in biological activity) overwhelmingly dominate chemesthetic detection, whereas both selective and "specific" processes (e.g., effects in which small structural changes in the VOC may evoke less predictable, and often large, changes in biological activity) control olfactory potency. To understand further the nature of the chemical factors that influence ODT values, we have explored here the possibility that NPT values could be used to estimate *selective* effects in ODTs, thus producing a tool to assess the weight of the remaining *specific* (VOC-receptor) effects. The topic opens the window to ponder why certain chemical families or particular compounds (and which ones) could have driven the need for a more specialized and sensitive chemoreception in humans. The present study involves data on 64 VOCs from various chemical series. The compounds are listed in our previous separate QSAR analysis of odor (Abraham et al., 2002) and nasal pungency (Abraham et al., 1998) thresholds. However, we give in Table 1 an updated list. In the next section we describe the QSAR model and illustrate further the meaning of the terms selective and specific within the present context.

Materials and Methods

Both odor and nasal pungency involve the transfer of a compound, for example a VOC, from an air stream through a mucus layer into a receptor or receptor area. This

environment is likely to be inhomogeneous, being partly a hydrophobic lipid-like area and partly a hydrophilic aqueous-like area. We have previously developed an equation, eq (1), that seems to be very satisfactory for the correlation and explanation of the transfer of VOCs from the gaseous phase to a large number of solvents or other condensed phases, including biophases (Abraham, 1993; Abraham et al., 2006a; Abraham et al., 2006b; Abraham et al., 2007).

$$SP = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + l \cdot \mathbf{L} \qquad (1)$$

In eq (1), **E**, **S**, **A**, **B**, and **L** are properties, or descriptors, of the VOC, and c, e, s, a, b, and l are regression coefficients, as described in detail previously (Abraham et al., 2004). Briefly, **E** is the excess molar refraction, **S** is the dipolarity/polarizability, and **A** and **B** are the overall or effective hydrogen bond acidity and basicity, respectively, of the VOC. **L** (log L^{16}) is defined through L^{16}, the VOC gas-hexadecane partition coefficient at 298 K, and is a measure of the lipophilicity of the VOC. In turn, the regression coefficients are not merely fitted coefficients since they define the complementary physicochemical properties that characterize the receptor environment or biophase most receptive to the VOC (Abraham, 1996). SP is either a physicochemical property of a VOC, such as log K where K is the gas to solvent partition coefficient for a series of VOCs into a given solvent or condensed phase; or a biological property of a VOC, such as an odor or nasal pungency threshold for a series of VOCs (Abraham et al., 2001).

When eq (1) was applied to NPTs, as log(1/NPT), a very good correlation that accounted for more than 95 % of the total effect was obtained (Abraham et al., 1998). This strongly suggests that the factors that influence NPTs are those that influence the transfer of VOCs from the gas phase to condensed phases, that is from the gas phase to the receptor phase, and that other effects are of secondary importance. However, when eq (1) was applied to ODTs, as log(1/ODT), a much poorer correlation was found (Abraham et al., 2002). Only by excluding families of compounds such as the aldehydes and carboxylic acids or by assigning a special descriptor to these families could a satisfactory correlation be obtained. Structural effects in transfer-type processes are invariably selective, in that different VOCs are transported from the gas phase to condensed phases

with different equilibrium constants that do not vary greatly with small changes in structure. The poor correlation observed for log (1/ODT) values suggests that they are partly influenced by transfer from the gas phase to the receptor phase, and are partly influenced by some type of specific effects.

In order to obtain more information on the factors that influence ODT values, we now explore the possibility that NPT values could be used to estimate the selective factors, that is to separate out the selective transport related effects and to leave only the specific effects. The present study involves data on 64 VOCs from various chemical series. The compounds are listed in our previous separate QSAR analysis of odor (Abraham et al., 2002) and nasal pungency (Abraham et al., 1998) thresholds.

Results and Discussion

ODTs and NPTs were correlated against Abraham's descriptors, using eq (1). The aim was to obtain a similar equation for both sets of data to make possible a comparison between them. To do so, compounds that were outliers in the equation for ODT, that is aldehydes and carboxylic acids, were left out in both cases. In addition four compounds that were outliers in the ODT equation and which might act through specific effects were omitted, viz: propanone, methyl acetate, t-butyl acetate and 1-octanol. Only the Abraham descriptors from eq (1) were used, without including any extra descriptor, or indicator variable. The resulting equations are:

$$\log(1/ODT) = -5.27(0.41) + 0.51(0.45)\,\mathbf{E} + 1.96(0.62)\,\mathbf{S} + 1.48(0.78)\,\mathbf{A} + 1.53(0.71)\,\mathbf{B} + 0.723(0.072)\,\mathbf{L} \quad (2)$$

$N = 50,\ R^2 = 0.780,\ SD = 0.57,\ F = 31.2$

$$\log(1/NPT) = -7.89(0.34) + 0.20(0.28)\,\mathbf{E} + 1.32(0.42)\,\mathbf{S} + 2.71(0.41)\,\mathbf{A} + 1.52(0.40)\,\mathbf{B} + 0.823(0.046)\,\mathbf{L} \quad (3)$$

$N = 38,\ R^2 = 0.916,\ SD = 0.28,\ F = 70.1$

In eq (2) and eq (3), N is the number of VOCs, R is the correlation coefficient, SD is the regression standard deviation, and F is the F-statistic. The SD values of the coefficients

themselves are in parentheses. The equation for the odor detection thresholds is still not very good, even omitting VOCs that might act by some specific effect. A detailed analysis of replicate ODT measurements suggests that the error in eq (2) is partly due to a lack-of-fit error and partly due to the error in the replicate measurements. As can be seen, all the coefficients, except the **A**-coefficient, are quite similar in eq (2) and eq (3), with the difference in the coefficients being no more than the sum of the errors of the coefficients. Hence NPT values are more affected by VOC hydrogen bond acidity than are the ODT values. The number of NPT values (N=38) is considerably less than the number of ODT values (N=50). In order to obtain a compound-by-compound comparison for all the ODT values, we therefore decided to use eq (3) to calculate log(1/NPT) values for all the VOCs for which we had ODT values. We refer to these as Clog(1/NPT) values (where "C" stands for "calculated").

We then regressed the observed values of log(1/ODT) against Clog(1/NPT) for the VOCs that we suggest act by selective effects only, and obtained eq (4).

$$\text{Log } (1/\text{ODT}) = 2.321 + 0.939\ \text{Clog}(1/\text{NPT}) \qquad (4)$$

$N = 50$, $R^2 = 0.747$, SD = 0.58, F = 141.7

If the **A**-descriptor is used as another independent variable, the regression improves slightly, as shown in eq (5).

$$\text{Log } (1/\text{ODT}) = 2.430 + 0.943\ \text{Clog}(1/\text{NPT}) - 0.955\ \mathbf{A} \qquad (5)$$

$N = 50$, $R^2 = 0.764$, SD = 0.57, F = 76.2

Both eq (4) and eq (5) reproduce the values of log (1/ODT) as well as does the full eq (2), for selectively acting VOCs. We can then use either equation as a 'base line' for selective effects, and can identify compounds that yield odor detection thresholds through a combination of selective and specific effects. This is illustrated in Figure 1, where we plot log (1/ODT) values for the 50 VOCs used in eq (4) and eq (5), plus aldehydes and acids, against calculated values from eq (5). The five aldehydes are more potent than calculated by an average of 1.7 log units, and the acids (excluding formic

acid) by an average of 3.0 log units. These are our estimates of the specific effect of the two series of VOCs. In our previous analysis of odor detection thresholds (Abraham et al., 2002) we were able to accommodate aldehydes and acids into general equations by adding an indicator variable that increased the potency of these compounds by 1.6 or 2.0 log units, depending on the exact form of the equation; the increased potency was for an average for the aldehydes and acids taken together. The present results for aldehydes and acids taken separately is in line with our previous analysis, but, we suggest, affords a much better estimate of the 'specific' effect on odor detection thresholds.

We can be reasonably sure that the aldehydes and acids provoke ODT through extra specific as well as selective effects because we have data for several other series for which we can calculate deviations from eq (5). We give in Table 2 values of the average error (AE), the absolute average error (AAE) and the standard deviation (SD) of the observed and calculated values for the various series. The key statistics are AE and AAE. The average error denotes deviation from eq (5), either in a positive or negative sense {AE = (calculated –observed values)/N where N is the number of data points}. If AE and AAE are compared, it is then possible to deduce whether a given value of AE is due to random deviations or systematic deviations from eq (5). For the first four series, the AE values are very small, so that there are no systematic deviations. The numerically larger AAE values then represent random deviations, as do the corresponding SD values. These range from 0.33 to 0.77 log units in accord with the SD value of 0.57 log units in eq (5). However, for the aldehydes and acids, AE is identical to AAE - all the deviations are of the same sign and are then systematic and not random. The SD value for the aldehydes is 3.6 times the SD in eq (5) and for the acids is 6.3 times the SD, so that the deviations from eq (5) are very large indeed. It is these systematic, not random, deviations from eq (5) that lead us to conclude that aldehydes and acids exert effects on ODTs through a combination of specific and selective effects.

We have used the term "specific effects" to describe the observation that aldehydes and acids are much more potent as regards odor detection thresholds than we calculate from our QSAR analysis. The nature of these specific effects is not obvious. They may be due to specific VOC-receptor interactions, but other possibilities exist. For example, it has been shown that odor binding proteins, OBPs, have a high affinity for

aldehydes and acids (Tcatchoff et al., 2006). Although the role of OBPs is not clear, we cannot exclude the possibility that aldehydes and acids are preferentially transported to the odor receptors.

For individual VOCs the position is not that straightforward. Of the four outliers that we have identified for ODTs, 1-octanol (2.15 obs, 0.41 calc) and tert-butyl acetate (-0.11 obs, -1.49 calc) are more potent than calculated through eq (5), but whether these effects are due, for example, to specific VOC-receptor interactions, rather than to error in either the ODT determinations or the descriptors is difficult to assess. Both methyl acetate (-3.46 obs, -2.06 calc) and propanone (-4.07 obs, -2.02 calc) are much less potent than calculated through eq (5); this cannot be due to any (extra) specific effect at all, and suggests that there are some factors that still need to be accounted for.

Now that we have used Clog(1/NPT) values to determined the specific effect of aldehydes and acids on ODT values, we can revert to log(1/NPT) values themselves in order to obtain a correlation between observed ODT values and observed NPT values for compounds that exert their influence through selective effects.

$$\text{Log}(1/\text{ODT}) = 3.562 + 1.282\ \log(1/\text{NPT}) \qquad (6)$$

$N = 34$, $R^2 = 0.819$, SD = 0.49, F = 144.5

$$\text{Log}\ (1/\text{ODT}) = 3.697 + 1.267\ \log(1/\text{NPT}) - 1.457\ \mathbf{A} \qquad (7)$$

$N = 34$, $R^2 = 0.867$, SD = 0.42, F = 101.1

Eq (6) can be used to predict further values of log (1/ODT) for VOCs that are thought to act through selective effects only; the SD value of only 0.49 log units is less than that in the full eq (2), although the latter is for 50 compounds. Unlike eq (4) and eq (5), there is now a substantial gain in goodness of fit if the **A**-descriptor is used as an independent variable, with the SD reduced to 0.42 log units. Hence eq (7) represents an even better predictive method. A plot of observed values of log (1/ODT) against those calculated on eq (7) is shown in Figure 2. Descriptor values are known for several thousand compounds (PharmaAlgorithms, 2006) and **A**-values are available for the prediction of log (1/ODT) values through eq (7) for numerous other VOCs. If not, it is possible to calculate **A**-values just from the structure of VOCs (PharmaAlgorithms, 2006), so that in most cases

eq (7) can be used for predictions. If an **A**-value is neither known nor is available, then eq (6) still represents a very good method for the prediction of further values. The quantitative relationship we have established between ODTs and NPTs for VOCs that act mainly via selective effects can facilitate the identification of outlying odorants for whom additional specific effects play a substantial role in their olfactory detection. These odorants could become prime candidates in the search of the best ligands for orphan ORs (Mizrahi et al., 2004). In addition, knowing the identity of these particularly powerful odorants can provide clues on the evolutionary factors that have driven the sense of smell to carve an enhanced sensitivity towards them (Niimura and Nei, 2006).

Finally, we can ask why we are able to use nasal pungency thresholds as a base line for selective effects in another biological end point altogether. Possible biological mechanisms of action of VOCs have been set out (Abraham et al., 1994) and we show in Figure 3 the 'two-stage' mechanism that was suggested. In the first stage the VOC is transferred from the vapor phase to a receptor phase or receptor area, and in the second stage the VOC activates a receptor. Now transfer from the vapor phase to typical organic phases involves selective effects, not specific effects. Thus if the main step in the mechanism of nasal pungency is the first stage, this would account for structural effects in the VOCs being selective only. We can obtain some information on this by comparing the coefficients in the selective NPT and ODT equations, eq (2) and eq (3), with those for transfer from the gas phase to various solvents (Abraham and Ibrahim, 2006b; Hoover et al., 2004) and biological phases (Abraham, 1993; Abraham and Ibrahim, 2006a; Abraham et al., 2005; Abraham et al., 2006a; Abraham et al., 2006b; Abraham et al., 2007). Details are in Table 3. The coefficients in these equations for transfer to solvents reflect the chemical properties of the solvent phases, so that the nearer one set of coefficients is to another set, the closer are the chemical properties of the phases. It is rather difficult to assess the closeness of sets of coefficients just by eye, and it is convenient to use principal components analysis (PCA). In this method, the five columns of coefficients, e to l, are transformed into five orthogonal columns of data (five PCs) that contain the same information as the original columns of coefficients. The first two PCs contain 80% of the total information, in the present case, and a plot of the scores of PC2 against PC1 will provide a visual estimate of how close are the sets of coefficients. The

coefficients for the phases investigated are in Table 3, and the PC plot is shown as Figure 4. The coefficients for the NPT and ODT equations are quite near to each other and to coefficients for transfer from the gas phase to biological phases (brain, muscle, liver) and organic solvents (wet 1-octanol, methanol, ethanol). All these solvents or phases have substantial values of the a- and b-coefficients. Transfer to all the solvents and biological phases shown in Table 3 involves selective, not specific, structural effects of the VOCs. Hence if the main step in a mechanism involves stage 1, or if only VOCs that act by selective effects are included, it is to be expected that the coefficients in the corresponding equations will be close to some particular solvent or biological phase. This is exactly what we find for the NPT or ODT equations. Of course the mechanism of nasal pungency, or odor, detection thresholds will involve VOCs passing from the gas phase through various layers of materials to the receptor phase (Rawson and Yee, 2006). But in an equilibrium situation, the overall equilibrium constant depends only on the concentrations in the initial phase (the gas phase) and the final phase (the receptor phase) – the intermediate phases in this context are irrelevant.

Conclusion

It is possible to separate out specific effects from selective effects in odor detection thresholds by the use of nasal pungency thresholds used as an indication of selective chemosensory effects. The main VOCs that show specific effects are the aldehydes and carboxylic acids, except for formic acid. Although this VOC appears 'normal' it is possible that this is a fortuitous combination of more than one specific effect. There are other VOCs that appear also to exhibit some specific effects as regards odor thresholds, and we can identify these as follows: 1-octanol, methyl acetate, propanone, and t-butyl acetate. Whether these VOCs really do exhibit some specific effects, or whether there is some possible experimental error is not clear – these five VOCs share no obvious common features. Eq (6) and particularly eq (7) represent excellent predictive methods for odor detection thresholds directly from observed nasal pungency detection thresholds. The correlation between NPT and ODT values for compounds that have only selective effects can be explained very satisfactorily by a two-stage mechanism of biological activity.

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Table 1 Compounds studied, their descriptors and values of log(1/ODT) and log(1/NPT)

Compound Name	**E**	**S**	**A**	**B**	**L**	log(1/ODT)	log(1/NPT)
Methanol	0.278	0.44	0.43	0.47	0.970	-3.18	-4.54
Ethanol	0.246	0.42	0.37	0.48	1.485	-1.85	-3.95
1-Propanol	0.236	0.42	0.37	0.48	2.031	-1.15	-3.40
2-Propanol	0.212	0.36	0.33	0.56	1.764	-2.70	-4.26
1-Butanol	0.224	0.42	0.37	0.48	2.601	-0.30	-3.04
2-Butanol	0.217	0.36	0.33	0.56	2.338	-1.98	-3.76
tert-Butyl alcohol	0.180	0.30	0.31	0.60	1.963	-2.78	-4.52
1-Pentanol	0.219	0.42	0.37	0.48	3.106	-0.11	-3.23
1-Hexanol	0.210	0.42	0.37	0.48	3.610	0.05	-2.60
1-Heptanol	0.211	0.42	0.37	0.48	4.115	1.00	-2.32
4-Heptanol	0.180	0.36	0.33	0.56	3.850	-0.91	-2.53
1-Octanol	0.199	0.42	0.37	0.48	4.619	2.15	-1.85
Methyl acetate	0.142	0.64	0.00	0.45	1.911	-3.46	-5.05
Ethyl acetate	0.106	0.62	0.00	0.45	2.314	-2.24	-4.83
Propyl acetate	0.092	0.60	0.00	0.45	2.819	-1.39	-4.24
Butyl acetate	0.071	0.60	0.00	0.45	3.353	-0.38	-3.56
sec-Butyl acetate	0.044	0.57	0.00	0.47	3.054	-0.57	-3.50
tert-Butyl acetate	0.025	0.54	0.00	0.47	2.802	-0.11	-3.98
Pentyl acetate	0.067	0.60	0.00	0.45	3.844	-0.07	-3.22
Hexyl acetate	0.056	0.60	0.00	0.45	4.290	0.20	-2.80
Heptyl acetate	0.050	0.60	0.00	0.45	4.796	0.01	-2.49
Octyl acetate	0.046	0.60	0.00	0.45	5.270	0.41	-1.95
Decyl acetate	0.041	0.60	0.00	0.45	6.240	0.50	
Dodecyl acetate	0.038	0.60	0.00	0.45	7.219	1.36	
2-Propanone	0.179	0.70	0.04	0.49	1.696	-4.07	-5.12
2-Pentanone	0.143	0.68	0.00	0.51	2.755	-0.93	-3.47
2-Heptanone	0.123	0.68	0.00	0.51	3.760	-0.27	-2.91
2-Nonanone	0.113	0.68	0.00	0.51	4.735	0.03	-2.53
Toluene	0.601	0.52	0.00	0.14	3.325	-2.19	-4.47
Ethyl benzene	0.613	0.51	0.00	0.15	3.778	-1.26	-4.00
Propyl benzene	0.604	0.50	0.00	0.15	4.230	-0.47	-3.17
Butyl benzene	0.600	0.51	0.00	0.15	4.730	-0.63	
Pentyl benzene	0.594	0.51	0.00	0.15	5.230	0.00	
Hexyl benzene	0.591	0.50	0.00	0.15	5.720	0.19	
Heptyl benzene	0.577	0.48	0.00	0.15	6.219	0.25	
Octyl benzene	0.579	0.48	0.00	0.15	6.714	0.43	
Butanal	0.187	0.65	0.00	0.45	2.270	-0.48	-4.77
Pentanal	0.163	0.65	0.00	0.45	2.851	-0.70	-4.57

Hexanal	0.146	0.65	0.00	0.45	3.357	1.10	-3.70
Heptanal	0.140	0.65	0.00	0.45	3.865	1.52	-3.13
Octanal	0.160	0.65	0.00	0.45	4.361	2.40	-3.24
Formic acid	0.343	0.75	0.76	0.33	1.545	-0.89	-2.50
Acetic acid	0.265	0.64	0.62	0.44	1.816	2.00	-1.62
Butanoic acid	0.210	0.64	0.61	0.45	2.750	2.44	-1.79
Hexanoic acid	0.174	0.63	0.62	0.44	3.697	2.59	-1.30
Octanoic acid	0.150	0.65	0.62	0.45	4.680	4.96	
Cumene	0.602	0.49	0.00	0.16	4.084	-0.03	-3.22
p-Cymene	0.607	0.49	0.00	0.19	4.590	-0.12	-3.05
Δ-3-Carene	0.511	0.22	0.00	0.10	4.649	-0.22	-3.21
Linalool	0.398	0.55	0.20	0.67	4.794	0.02	-2.55
1,8-Cineole	0.383	0.33	0.00	0.76	4.688	0.49	-2.37
Geraniol	0.513	0.54	0.35	0.63	5.510	1.05	
α-Terpinene	0.526	0.25	0.00	0.15	4.715	-0.15	-3.30
γ-Terpinene	0.497	0.32	0.00	0.20	4.815	-0.99	
α-Pinene	0.446	0.14	0.00	0.12	4.308	-1.28	
β-Pinene	0.530	0.24	0.00	0.19	4.394	-1.07	
(R)-(+)- Limonene	0.488	0.28	0.00	0.21	4.725	-0.99	
(S)- (-)-Limonene	0.488	0.28	0.00	0.21	4.725	-0.66	
β-Phenyl ethyl alcohol	0.811	0.86	0.31	0.65	4.628	2.19	
Pyridine	0.631	0.84	0.00	0.52	3.022	-0.11	-3.11
Menthol	0.400	0.50	0.23	0.58	5.177	1.66	-1.71
1-Octene	0.094	0.08	0.00	0.07	3.568	-2.31	
1-Octyne	0.155	0.22	0.09	0.10	3.521	-2.13	-4.49
Chlorobenzene	0.718	0.65	0.00	0.07	3.657	-1.11	-4.02

Table 2. Deviations from eq (5) for various series

Series	N	AE	AAE	SD
Alcohols	11	-0.06	0.69	0.77
Acetates	10	0.04	0.43	0.53
Ketones	3	0.11	0.26	0.33
Alkyl benzenes	8	-0.27	0.35	0.45
Aldehydes	5	1.70	1.70	2.05
Acids	4	3.04	3.04	3.57

Table 3 Coefficients in equations for gas to solvent or phase transfer

Solvent or phase	No	c	e	s	a	b	l
log(1/NPT)	1	-7.89	0.20	1.32	2.71	1.52	0.823
log(1/ODT)	2	-5.27	0.51	1.96	1.48	1.53	0.723
Blood, 37^{o}C	3	-1.07	0.46	1.08	3.74	2.58	0.376
Brain, 37 ^{o}C	4	-0.99	0.26	0.41	3.36	2.03	0.591
Muscle, 37 ^{o}C	5	-1.04	0.21	0.72	3.24	2.47	0.463
Liver, 37 ^{o}C	6	-0.92	0.08	0.77	2.79	2.09	0.560
Fat, 37 ^{o}C	7	-0.05	0.05	0.73	1.78	0.33	0.743
Olive oil 37 ^{o}C	8	-0.16	-0.25	0.86	1.66	0.00	0.873
1-Octanol	9	-0.20	0.00	0.71	3.52	1.43	0.858
Methanol (dry)	10	0.00	-0.22	1.17	3.70	1.43	0.769
Ethanol (dry)	11	0.01	-0.21	0.79	3.64	1.31	0.853
1-Butanol (dry)	12	-0.04	-0.28	0.54	3.78	1.00	0.934
1-Octanol (dry)	13	-0.12	-0.20	0.56	2.56	0.70	0.939
N-Methylformamide(dry)	14	-0.60	-0.26	2.00	4.56	0.43	0.706
Ethyl acetate (dry)	15	0.20	-0.34	1.25	2.95	0.00	0.917
Acetone (dry)	16	0.15	-0.28	1.52	3.26	0.00	0.863
Ether (dry)	17	0.21	-0.17	0.87	3.40	0.00	0.882
Acetonitrile (dry)	18	-0.01	-0.60	2.46	2.09	0.42	0.738
Chloroform	19	0.12	-0.47	1.20	0.14	1.43	0.994
Ethylene glycol (dry)	20	-0.90	0.22	1.43	4.47	2.69	0.568
Hexadecane	21	0.00	0.00	0.00	0.00	0.00	1.000
Cyclohexane	22	0.16	-0.11	0.00	0.00	0.00	1.013
Toluene	23	0.12	-0.22	0.94	0.47	0.10	1.012

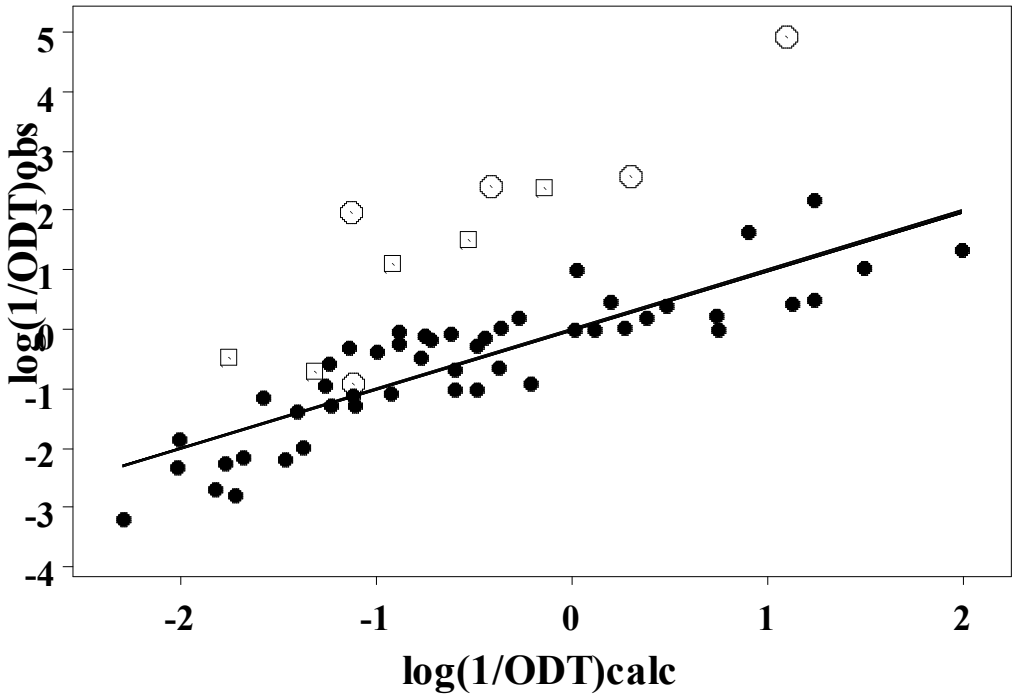

Figure 1. A plot of log(1/ODT)obs against log(1/ODT) calculated on eq (5), showing the "specific" effects of aldehydes and acids ○. The regression line is for the selective compounds.

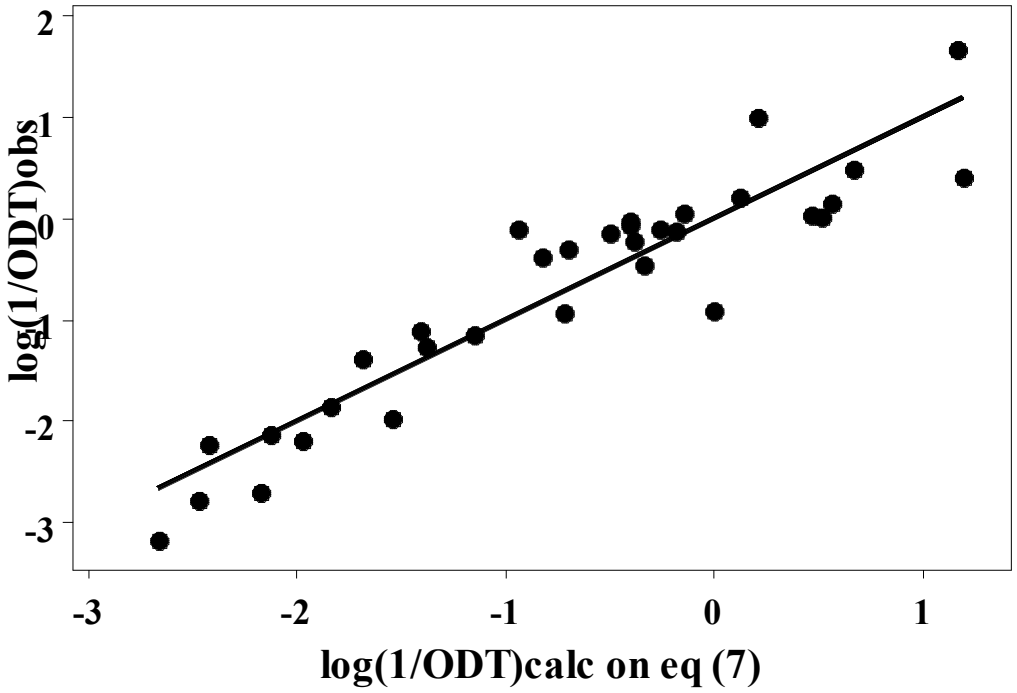

Figure 2. A plot of log(1/ODT)obs against log(1ODT)calc on eq (7)

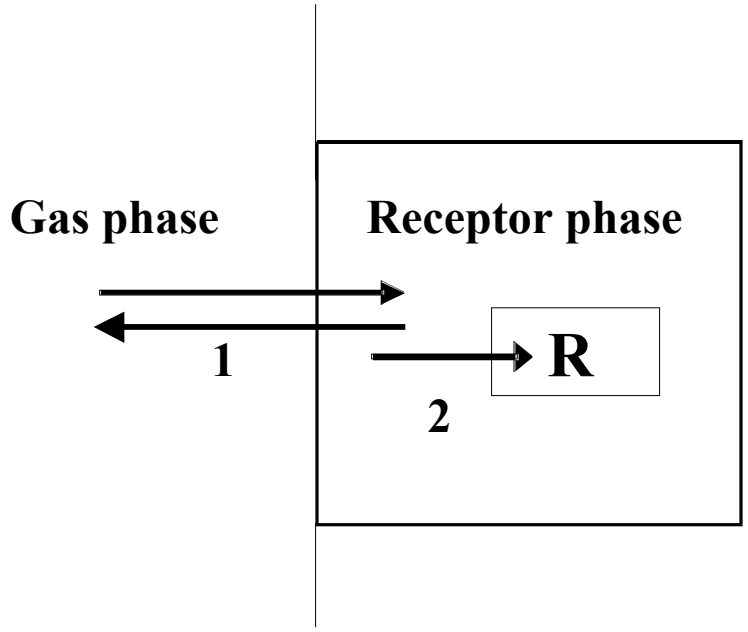

Figure 3. The two-stage mechanism of biological activity of VOCs.

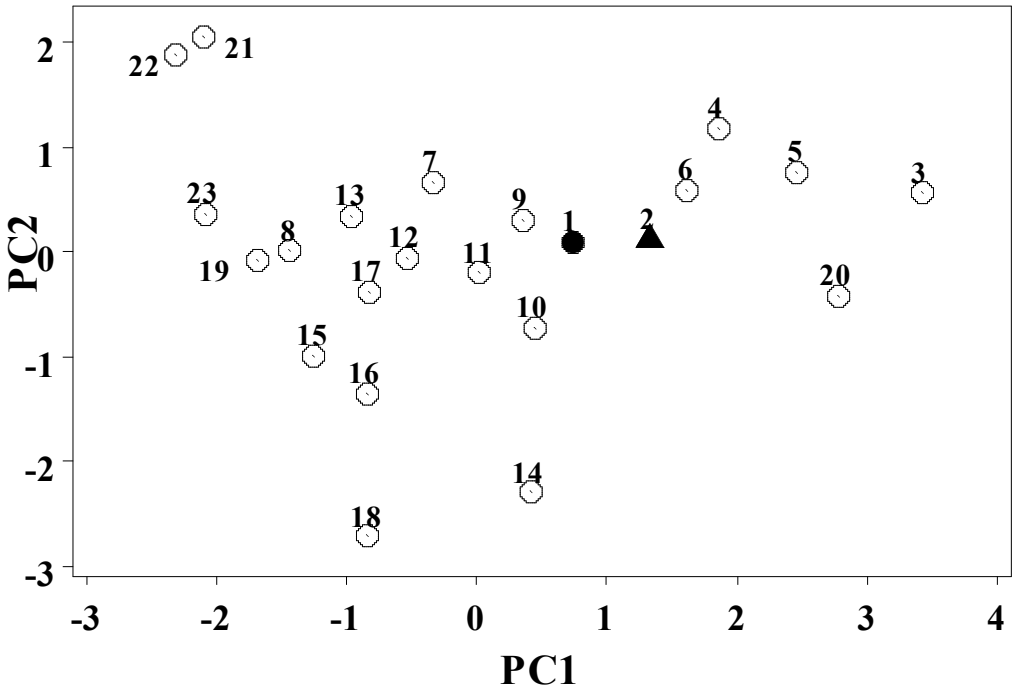

Figure 4. A plot of the scores of PC2 against the scores of PC1. Points numbered as in Table 3: ● NPT, ▲ODT.

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