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Physico-chemical modelling of sensory irritation in humans and experimental animals

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Chapter Title: Physico-chemical modelling of sensory irritation in humans and experimental animals

Running Head: Modelling of Sensory irritation

Index

Introduction

Upper respiratory tract irritation in mice

Nasal pungency thresholds in man

Introduction

Chemosensory detection of volatile organic compounds, VOCs, by humans rests on the senses of smell and sensory irritation, being both part of the body warning system. Several terms have been employed that subsume the sensations evoked by chemicals that are typically viewed as irritative. For example, in 1912, Parker introduced the concept of the “common chemical sense” (CCS) to describe general mucosal sensitivity to chemicals (1,2). More recently, the terms “chemesthesis” and “pungency” have been used to describe sensations evoked by chemicals that are not properly odours. Such pungency includes: piquancy, tingling, prickling, irritation, stinging, burning, and freshness, among others.

The sense of smell gives rise to the perception of odours, whereas chemesthesis gives rise to the perception of pungency. Whereas odours are detected in the olfactory mucosa that covers the upper back portion of the nasal cavity via the olfactory nerve (cranial nerve I), chemesthetic sensations are mainly detected in all three mucosa: ocular, nasal, and oral, mainly via the trigeminal nerve (cranial nerve V) (3). The pharmacological and toxicological characterization of the senses of smell and chemesthesis includes the study of the breadth and sensitivity of responses towards the spectrum of chemicals. Recent studies on the molecular biology of smell (4) have

provided additional support to the long-held view of the existence of a large number of different odorant receptors, probably in the order of 800 in humans, of which about half are functional (5). Since a given odorant can activate more than one type of receptor, and since a given type of receptor can be activated by several odorants, the number of possible odorants that can be recognised may reach several million (6,7). Of course, odour detection is another matter altogether, and within the context of odour detection, a systematic strategy to study the breadth of chemical tuning and sensitivity in olfaction and chemesthesis has considerable merit. One strategy to uncover the physicochemical basis for odour detection thresholds and pungency thresholds of VOCs consists of measuring chemosensory thresholds for homologous series of compounds. Over the past twenty years, Cometto-Muñiz and co-workers have carried out a systematic investigation into thresholds for sensory irritation and odour, using panels of human subjects under carefully controlled conditions and homologous series of compounds, including alcohols, esters (acetates), ketones, aldehydes, carboxylic acids, aromatic hydrocarbons, and terpenes.

Previous research has shown that olfaction is more sensitive than chemesthesis in the detection of VOCs (8). One approach to avoid the influence of smell is to probe nasal chemosensory detection in participants lacking olfaction, that is anosmics. Another approach consists in testing participants with an intact olfaction, that is, normosmics, but in terms of nasal localization or lateralization rather than detection. This technique tests the ability of subjects to identify the nostril receiving the VOC when the contralateral nostril simultaneously receives plain air (9), and it has been shown that such localization is mediated by trigeminal, not olfactory input (10).

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 allows the study of VOCs that are too toxic to be tested on humans, but, again, the number of VOCs that can be tested on animals is but a small fraction of the number of VOCs that are actual or potential irritants.

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’ or ‘non-reactive’ 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 be encountered. We define and explain the terms ‘non-reactive’ and ‘reactive’ in the section “Upper respiratory tract irritation in mice.”

As mentioned, irritant VOCs comprise a very diverse group of compounds and the structural basis of their activity is not well understood. Nerve recordings (11) and human psychophysical studies (12, 13) indicate that response thresholds are strongly related to hydrophobicity within homologous series. The high correlation between hydrophobicity and pungency has led to the suggestion that irritants interact with a hydrophobic biophase (14), either the epithelium through which irritants must diffuse or the nerve ending itself.

The trigeminal nerve fibers reaching the nasal mucosa ramify repeatedly, terminating in free nerve endings (15). Trigeminal nerve fibers that respond to irritating compounds, contain the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) and extend close to the nasal epithelia surface (16). Electron microscopic studies suggest that the vast majority of the CN V free nerve endings terminate within the lamina propria. Nevertheless, a few trigeminal fibers terminate at

the line of tight junctions only a few micrometers from the surface (16). For volatile chemicals to stimulate these nerve endings, they must (1) pass into the nasal cavity, (2) partition into and diffuse through the mucus, and (3) cross the epithelial membranes and/or intercellular tight junctions.

Several mechanisms have been proposed to explain how irritative chemicals initiate transduction at the surface of cell membranes (17) although the nature of these processes is still poorly understood. Compounds that are chemically reactive, that is their potency is induced by a chemical mechanism, (18) can produce irritation directly by reacting with a receptor or indirectly by mucosal tissue damage via chemical reaction without the need to interact with any particular receptor (17). In the latter case, damaged cells would release endogenous chemicals such as ATP, H^+ , and bradykinin (a nonapeptide messenger) which, in turn, could act specifically upon ion channels to produce the neural response (19, 20). On the other hand, there are other compounds that are likely to act on specific receptors such as menthol (21), capsaicin (22), and nicotine (23).

Studies of homologous series of irritant VOCs shed light on the contribution of the chemical structure in their interactions with receptors. Inoue and Bryant (24) found that (1) longer chain aldehydes and alcohols activate neurons at lower concentration than their shorter homologous, while chain length does not affect enaldehyde responses; (2) aldehydes are more active, stimulating more neurons than the same concentration of corresponding alcohols; (3) the presence of a double bond in enaldehydes increases the number of neurons that respond to lower concentration than corresponding aldehydes; (4) the three homologous series activate a subpopulation of capsaicin-sensitive nociceptors (25), and partially activate a TRPA1-bearing subpopulation of nociceptors, enough to cause pungency, as mustard oil activation of TRPA1 does (26).

Some of these findings are in very good agreement with those by Cometto-Muñiz and co-workers. For instance, odor detection thresholds, ODTs and nasal pungency thresholds, NPTs, decrease when the chain length increases (12). Cometto-Muñiz and co-workers also reported lower threshold values for aldehydes than alcohols (13). These findings are also consistent with those of Alarie and co-workers (18), since they demonstrate that enaldehydes have lower irritation thresholds in mice than the corresponding saturated aldehydes.

Methods for the determination of NPTs in humans have been described in the Chapter “Nasal chemosensory irritation in humans”, but there has also been considerable work on the effect of VOCs on upper respiratory tract irritation in mice, which requires a different experimental methodology. The most sophisticated method is that due to Alarie and co-workers who have described it in some detail (27, 28). An all-glass exposure chamber holds four mice, the bodies of which are held in plethysmographs connected to a pressure transducer. The head of each mouse projects into the chamber, and a constant flow of air containing a known concentration of a chemical is passed through the chamber. The plethysmograph / pressure transducer records the respiratory rate of the mouse, and the biological endpoint is taken as the concentration of chemical that leads to a 50% decrease in respiratory rate, denoted as RD₅₀. The first quantitative structure-activity relationships for irritation of vapors were constructed using the RD₅₀ endpoint in mice, and it is this work that we first consider, before the work of Cometto-Muñiz and Cain on nasal pungency thresholds in humans.

Upper respiratory tract irritation in mice

A great deal of work on upper respiratory tract irritation in mice has been carried out by Alarie and co-workers, who not only developed a rigorous experimental procedure to

obtain values of RD_{50} that is an ASTM standard (29), but who also showed that the mouse bioassay could be used to estimate acceptable exposure levels in man (30-33). Kuwabara and co-workers (34) have also reviewed the use of RD_{50} values to determine acceptable exposure levels in man. Not surprisingly, there have been numerous attempts to correlate RD_{50} values with various physico-chemical properties of VOCs.

Much of the early work revolved around the suggestion of Ferguson (35) that for VOCs that acted by a ‘physical’ mechanism, there was a correlation between the gaseous toxic concentration and solubility or vapor pressure. Brink and Pasternak (36) considered the ratio P^{nar}/P^0 , where P^{nar} is the gaseous narcotic partial pressure of a VOC in some particular bioassay and P^0 is the saturated vapor pressure of the VOC, and referred to the ratio as the ‘thermodynamic activity’. They put forward the rule of equal narcotic activity at equal thermodynamic activity; in other words, the ratio P^{nar}/P^0 is constant. The Ferguson-Brink-Pasternak (FBP) rule was extended to cover not just gaseous narcosis, but gaseous bioassays in general, as in eqn (1).

$$P^{bioassay}/P^0 = c \quad (1)$$

It was never very clear how the FBP rule, eqn (1), could be regarded as a thermodynamic rule, because in practise it was not actually constant. For example, Nielsen and Alarie (32) obtained the data shown in Table 1 for a series of alkylbenzenes. The ratio RD_{50}/P^0 is only approximately constant. Abraham and co-workers (37) then showed that there was no thermodynamic basis for the FBP rule at all, but that it was just a useful empirical observation.

Table 1. The FBP rule for some alkylbenzenes (32)

VOC	RD_{50} in ppm	P^0 in ppm at 37oC	RD_{50}/P^0

Toluene	5300	73000	0.073
Ethylbenzene	4060	29400	0.138
n-Propylbenzene	1530	11100	0.138
Isopropylbenzene	2490	12700	0.196
n-Butylbenzene	710	5600	0.126
tert-Butylbenzene	760	8600	0.088
n-Pentylbenzene	230	1020	0.226
tert-Butyltoluene	360	2050	0.176
n-Hexylbenzene	125	359	0.349

Nevertheless, several analyses of RD_{50} values have used the VOC vapor pressure or normal boiling point. Muller and Gref (38) analysed four series of VOCs: ketones, alcohols, acetates and various benzene derivatives. For each individual series, they showed correlations between $\log(1/RD_{50})$ and various physico-chemical properties such as the water to octanol partition coefficient, and the normal boiling point, T_B . However, since each series was analysed separately, it is doubtful if the various correlations have any mechanistic significance. The importance of the work is only to show that it is possible to connect values of RD_{50} (or $\log 1/RD_{50}$) to physico-chemical properties.

Roberts (39) also analysed the four series of compounds separately, but was able to generate a general QSAR covering 42 saturated ketones, saturated alcohols and aromatic compounds, eqn (2);

$$\text{Log}(M/RD_{50}) = 0.0173 T_B - 4.090 \quad (2)$$

$$N = 42, SD = 0.119, R^2 = 0.974$$

In eqn (2), M is the molecular weight of the VOC and T_B' is an adjusted normal boiling point taken as $(26.5 T_B / 22) - 8$ for the alcohols, and $(24.0 T_B / 22) - 4$ for phenol; all the other compounds have $T_B' = T_B$ itself. N is the number of data points, that is the number of VOCs, SD is the standard deviation, and R is the correlation coefficient. Five compounds were omitted from eqn (2): allyl alcohol, methyl vinyl ketone, crotyl alcohol, mesityl oxide and vinyl toluene. Roberts pointed out that the excess potency of the first four compounds could be due to their reactive electrophilic character, and subsequent work seems to confirm this. Also omitted from eqn (2) was a series of acetate esters. Roberts suggested that these esters were hydrolysed to the corresponding alcohol and acetic acid, the latter being a much more potent irritant.

Even for non-reactive compounds, the problem with eqn (2) concerns the adjusted normal boiling point, which is a purely empirical correction. It is impossible to use eqn (2) to predict further values of RD_{50} , outside the series of saturated ketones and saturated alcohols, because the adjustment itself cannot be predicted.

Nielsen and Alarie (32) showed that for a series of alkylbenzenes and a series of aliphatic alcohols, the FBP ratio was roughly constant, see Table 1.

The publication of an important data base of RD_{50} values by Schaper (40) led to the analysis of a much larger number of RD_{50} values than had hitherto been possible. Alarie and co-workers (18) used the FBP rule to divide a data base of 145 VOCs into those that acted by a 'physical' mechanism (non-reactive VOCs) and for which $P^{\text{bioassay}}/P^0 > 0.1$, and those that acted by a 'chemical' mechanism (reactive VOCs) and for which $P^{\text{bioassay}}/P^0 < 0.1$ (the bioassay being the RD_{50} value). The division into non-reactive and reactive VOCs based on $P^{\text{bioassay}}/P^0 > 0.1$ or < 0.1 is arbitrary, but there will always be an arbitrary element in such a division – how much more reactive than expected does a

VOC have to be before being assigned to the ‘reactive’ class? They later showed (41) that for 50 non-reactive VOCs, a reasonable correlation of $\log RD_{50}$ against $\log P^0$ was obtained:

$$\log RD_{50} = 0.844 \log P^0 + 2.634 \quad (3)$$

$$N = 50, SD = 0.257, R^2 = 0.89$$

In their analysis of the FBP equation, Abraham and co-workers (37) set out various models for the biological activity of gaseous compounds, and showed that experimental observations could be analysed through the simple model illustrated in Figure 1. The VOC is transferred from the gas phase to a receptor phase or receptor area in step 1, and then the VOC interacts with the receptor in step 2. For non-reactive compounds, step 1 was the most important in upper respiratory tract irritation in mice (37), and subsequently was shown also to be the main step in inhalation anesthesia (42). Since the main step involves the transfer of a VOC from the gas phase to a receptor phase, Abraham and co-workers (37) argued that it should be possible to discover a gas phase to solvent process that was a good model for stage 1. The appropriate physico-chemical factor is K (sometimes denoted as L), the gas to solvent partition coefficient defined through eqn 4; K is then dimensionless.

$K =$ concentration in solvent at equilibrium in mol dm^{-3} / concentration

$$\text{in the gas phase at equilibrium in } \text{mol dm}^{-3} \quad (4)$$

It was then shown that the solvents tri(2-ethylhexyl)phosphate and N-formylmorpholine were good models for upper respiratory tract irritation in male Swiss OF₁ mice, wet octanol was not quite such a good model, and water was a very poor model (37, 43).

Nielsen and co-workers (44) correlated $\log RD_{50}$ values against $\log K$ for solubility of gaseous compounds in wet octanol, but only for a restricted set of VOCs, and also

used the water to octanol partition coefficient, as $\log P_{oct}$, as a descriptor; other workers did likewise (45), again for a very restricted set of VOCs.

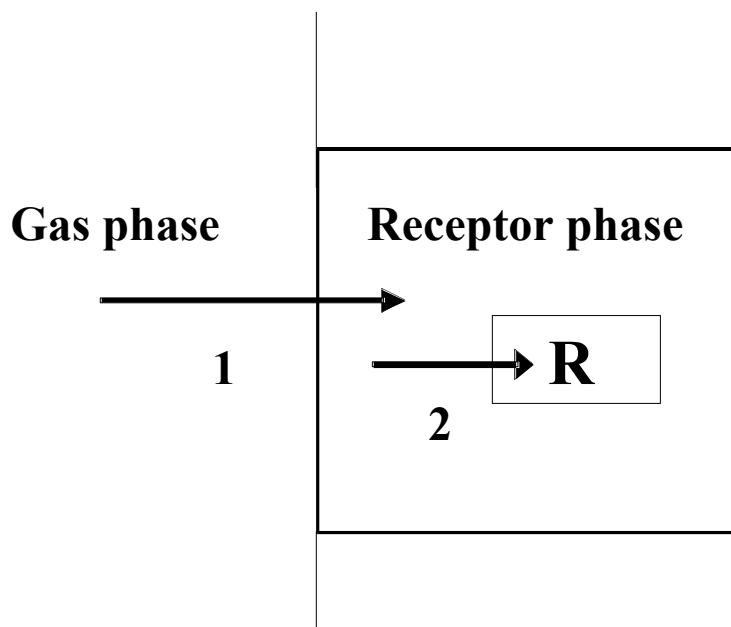


Figure 1. The two step mechanism proposed by Abraham and co-workers (37).

The first really general QSAR for RD_{50} values used a multiple linear regression analysis, MRLA, to correlate $\log (1/ RD_{50})$ against a number of independent variables, or descriptors (46):

$$\text{Log} (1/ RD_{50}) = 0.60 + 1.35 S + 3.19 A + 0.77 L \quad (5)$$

$$N = 39, SD = 0.10, R^2 = 0.98$$

The independent variables in eqn (5) were S the VOC dipolarity/polarizability, A the VOC overall hydrogen bond acidity, and L the logarithm of the gas to hexadecane partition coefficient at 25°C. Note that in eqn (5) the units of RD_{50} were mol dm^{-3} , so that the constant term is quite different to that in equations where RD_{50} is in ppm. The independent variables have more recently been discussed in depth (47). Eqn (5) is consistent with the analysis of Abraham and co-workers (37) of the biological activity

of gases and their suggestion that solubility of gases in solvents could be a possible model, because equations on the lines of eqn (5) have been shown to account for the solubility of gases in a variety of solvents (47).

Alarie and co-workers (41) expanded eqn (5) to include 50 non-reactive VOCs as in eqn (6), and also constructed a number of other, slightly less successful QSARs.

$$\text{Log}(1/\text{RD}_{50}) = -6.834 + 1.280 S + 2.230 A + 0.764 L \quad (6)$$

$$N = 50, SD = 0.244, R^2 = 0.91$$

A slightly larger data base led to eqn (7) with somewhat less satisfactory statistics.

$$\text{Log}(1/\text{RD}_{50}) = -7.049 + 1.437 S + 2.316 A + 0.774 L \quad (7)$$

$$N = 58, SD = 0.354, R^2 = 0.84$$

The most recent analysis of RD_{50} values is by Luan and co-workers (48) who used a number of methods to classify VOCs into reactive and non-reactive groups, and to correlate $\log(\text{RD}_{50})$ for 59 non-reactive VOCs. They start by calculating about 612 theoretical descriptors for each VOC, and reduce them to a pool of 166 descriptors. The 'best' set of descriptors from the pool of 166 were chosen for a linear correlation of 47 of the non-reactive VOCs:

$$\begin{aligned} \text{Log}(\text{RD}_{50}) = & 5.50 - 0.043 Re - 6.329 RPCG - 0.377 IC_{ave} - 0.049 CH_{donor} + 3.826 \\ & RNSB - 0.047 ZX \end{aligned} \quad (8)$$

$$N = 47, SD = 0.362, R^2 = 0.844$$

The meaning of the six descriptors is given in Table 2. Although eqn (8) is more complicated, and much more difficult to interpret in a chemical way, than eqn (6) and eqn (7), it is statistically no more successful. Luan and co-workers (48) then used eqn (8) to predict values for 12 non-reactive VOCs that had not been used to set up eqn (8). In Table 3 are given the statistics for the predictions in terms of AE the average error, AAE the absolute average error, RMSE the root mean square error and SD the standard

deviation; this is the first time (48) that the predictive ability of any equation for RD_{50} has been assessed. In Table 3, this linear model is denoted as LM.

Luan and co-workers (48) also used two non-linear methods to analyse 47 of the non-reactive compounds, one method is based on a support vector machine, SVM, and the other method is a radial basis function neural network, RBFNN. Details of the predictions for the 12 non-reactive VOCs used as a test set are in Table 3. Results are somewhat better than those from eqn (8). Unfortunately, it is not possible to compare the SVM and RBFNN methods with the linear eqn (6) or eqn (7) in any exact way, but the non-linear methods do not seem to be very much better than the linear method in the correlation of $\log(RD_{50})$ values for non-reactive VOCs.

However, for the classification of 142 VOCs into a set of reactive and a set of non-reactive compounds, the non-linear SVM method was much superior to linear methods. For 28 test compounds, the linear method correctly classified 75% of the VOCs, whereas the SVM method correctly classified 85.7%. This is the first time that VOCs have been classed as non-reactive or reactive without use of the FBP rule.

Table 2. The independent variables (descriptors) used by Luan and co-workers.

Descriptor	Chemical meaning (48)
<i>Re</i>	Refractivity
<i>RPCG</i>	RPCG relative positive charge
<i>IC_{ave}</i>	Average information content (order 2)
<i>CH_{donor}</i>	Count of H-donor sites
<i>RNSB</i>	Relative number of single bonds
<i>ZX</i>	ZX shadow

Table 3. Statistics for the prediction of log (RD₅₀) for 12 non-reactive VOCs (48)

Method	<i>AE</i>	<i>AAE</i>	<i>RMSE</i>	<i>SD</i>
LM	-0.148	0.358	0.507	0.529
SVM	-0.084	0.348	0.452	0.472
RBFNN	-0.081	0.346	0.480	0.501

Nasal pungency thresholds in man

Nasal pungency involves the transfer of a compound, for example a VOC, from an air stream through a mucus layer into a receptor or receptor area, and interaction of the VOC with the receptor. The model set out by Abraham and co-workers (29), Figure 1, thus seems appropriate for the analysis of nasal pungency thresholds, NPTs. Abraham and co-workers (47) have devised a linear free energy relationship, LFER, and have applied it to the correlation of the solubility of gases in various solvents and biological phases. Since the first step of the model, Figure 1, involves the solubility of VOCs in the receptor area, it seems logical to apply the LFER to values of nasal pungency thresholds. The LFER can be stated as in eqn (9)

$$SP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + l \cdot L \quad (9)$$

In eqn (9), *E*, *S*, *A*, *B*, and *L* are independent variables that are properties, or descriptors, of the VOC, and *c*, *e*, *s*, *a*, *b*, and *l* are regression coefficients determined by multiple linear regression. The equation has been described in detail previously (47). Briefly, *E* is the excess molar refraction, *S* is the dipolarity/polarizability, *A* and *B* are the overall or effective hydrogen bond acidity and basicity, respectively, of the VOC, and *L* is defined as the logarithm of the VOC gas-hexadecane partition coefficient at 298 K, which is a measure of the lipophilicity of the VOC. The regression coefficients in eqn (9) are not merely fitted coefficients since they define the complementary physicochemical properties that characterize the receptor environment or biophase most receptive to the VOC (47). The dependent variable, 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 a nasal pungency threshold for a series of VOCs, in the form of $\log(1/\text{NPT})$. The reciprocal is used so that the larger is $\log(1/\text{NPT})$, the more potent is the VOC.

The values of NPT, or $\log(1/\text{NPT})$, for a variety of VOCs have been determined by Cometto-Muñiz and Cain as reported in the Chapter “Nasal chemosensory irritation in humans”. When eqn. (9) was applied to NPTs as $\log(1/\text{NPT})$, a very good correlation that accounted for 95 % of the total effect was obtained (49), see eqn (10). The term in *e.E* was not significant and was left out. Eqn (10) 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 VOC-receptor interactions are of secondary importance.

$$\text{Log}(1/\text{NPT}) = - 8.562 + 2.209 S + 3.417 A + 1.535 B + 0.865 L \quad (10)$$

$N = 34, R^2 = 0.953, SD = 0.27, F = 144$

A recent equation, based on 47 VOCs, rather than the 34 VOCs in eqn (10) is shown as eqn (11). Values of the descriptors and of the $\log(1/\text{NPT})$ values are in Table 4.

$$\text{Log}(1/\text{NPT}) = - 7.770 + 1.543 S + 3.296 A + 0.876 B + 0.816 L \quad (11)$$

$N = 47, R^2 = 0.901, SD = 0.312, F = 95, Q^2 = 0.874, \text{PRESS} = 5.1901, \text{PSD} = 0.351$

There are not enough data points in Table 4 to divide them into a training set and a test set. Hawkins (50) suggests that assessment of predictive ability using a test set are unreliable unless the set contains at least 50 data points – compare the test set of only 12 compounds used by Luan and co-workers (48), above.

It has been shown that statistics based on the leave-one-out method yield a reasonable assessment of predictive ability (51), even though based on the total data set. The leave-one-out statistics are Q^2 , PRESS, and PSD the ‘predictive’ standard deviation as explained in detail (51). In eqn (11), $\text{PSD} = 0.35$ log units, and this can be taken as an assessment of the predictive capability of eqn (11). A plot of calculated values of $\log(1/\text{NPT})$ on eqn (11) against the observed values is shown in Figure 2; there is random scatter about the line of best fit.

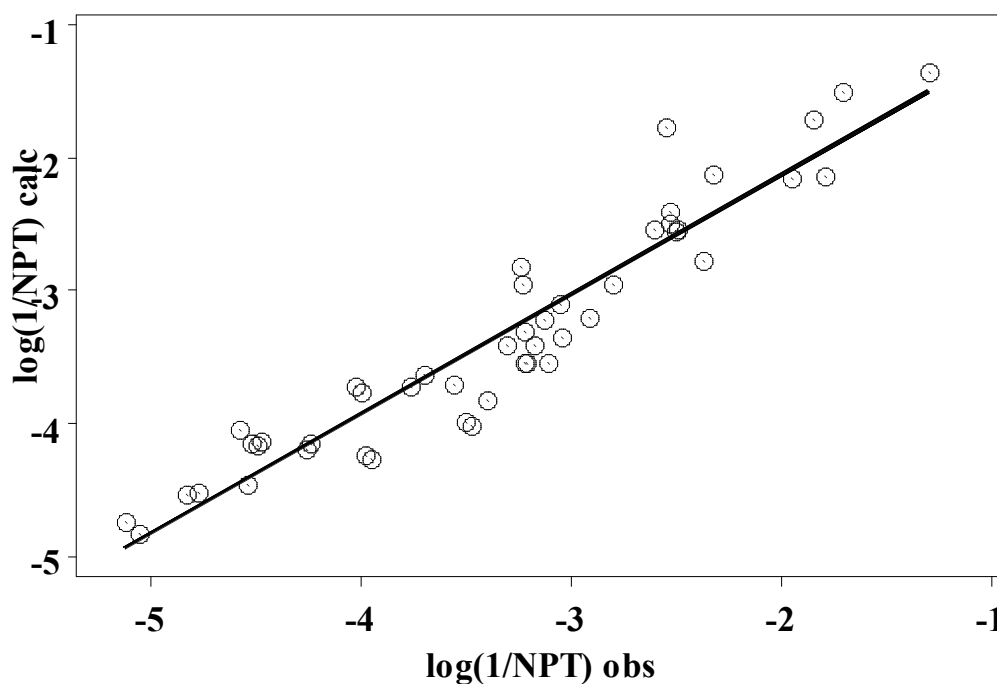


Figure 2. A plot of calculated values of $\log(1/\text{NPT})$ on eqn (11) against the observed values of $\log(1/\text{NPT})$.

A remarkable feature of the equations for $\log(1/\text{NPT})$ is that they include carboxylic acids, aliphatic aldehydes and the lower alkyl acetates, all of which are regarded as reactive compounds in the mouse bio-assay (18, 41, 43). The reasons why these VOCs behave as non-reactive compounds in the sensory irritation assay in man and as reactive compounds in upper respiratory tract irritation in mice are not clear.

Table 4. VOC descriptors used in eqn (11)

VOC	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>L</i>	SP ^a
Methanol	0.278	0.44	0.43	0.47	0.970	-4.54
Ethanol	0.246	0.42	0.37	0.48	1.485	-3.95
Propan-1-ol	0.236	0.42	0.37	0.48	2.031	-3.40
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	-3.04
Butan-2-ol	0.217	0.36	0.33	0.56	2.338	-3.76
tert-Butyl alcohol	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	-3.23
Hexan-1-ol	0.210	0.42	0.37	0.48	3.610	-2.60
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	-1.85
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
sec-Butyl acetate	0.044	0.57	0.00	0.47	3.054	-3.50
tert-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	4.290	-2.80
Heptyl acetate	0.050	0.60	0.00	0.45	4.796	-2.49
Octyl acetate	0.046	0.60	0.00	0.45	5.270	-1.95
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	0.113	0.68	0.00	0.51	4.735	-2.53
Toluene	0.601	0.52	0.00	0.14	3.325	-4.47
Ethyl benzene	0.613	0.51	0.00	0.15	3.778	-4.00
Propyl benzene	0.604	0.50	0.00	0.15	4.230	-3.17
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	0.343	0.75	0.76	0.33	1.545	-2.50
Butanoic acid	0.210	0.64	0.61	0.45	2.750	-1.79
Hexanoic acid	0.174	0.63	0.62	0.44	3.697	-1.30
Cumene	0.602	0.49	0.00	0.16	4.084	-3.22
p-Cymene	0.607	0.49	0.00	0.19	4.590	-3.05
Δ -3-Carene	0.511	0.22	0.00	0.10	4.649	-3.21
Linalool	0.398	0.55	0.20	0.67	4.794	-2.55
1,8-Cineole	0.383	0.33	0.00	0.76	4.688	-2.37
α -Terpinene	0.526	0.25	0.00	0.15	4.715	-3.30
Pyridine	0.631	0.84	0.00	0.52	3.022	-3.11
Menthol	0.400	0.50	0.23	0.58	5.177	-1.71
Oct-1-yne	0.155	0.22	0.09	0.10	3.521	-4.49
Chlorobenzene	0.718	0.65	0.00	0.07	3.657	-4.02

^a Log (1/NPT)

There have been a few other QSARs constructed for the correlation of NPTs. Famini and co-workers (52) obtained the linear relationship, eqn (12) for 42 VOCs, with a statistical fit about the same as eqn (11).

$$\text{Log}(1/\text{NPT}) = -16.40 + 2.258 V_{mc} + 3.471 q^- + 50.56 \varepsilon_\alpha + 13.63 q^+ \quad (12)$$

$$N = 42, R^2 = 0.923, SD = 0.357, F = 110, Q^2 = 0.885$$

In eqn (12), V_{mc} is a molecular volume, q^- is the absolute value of the most negative formal charge on the VOC (equivalent to the electrostatic basicity), ε_α is a covalent acidity term, and q^+ is the partial charge of the most positive hydrogen in the VOC (equivalent to the electrostatic acidity). Although the formalism differs from that used in eqn (11), the terms in eqn (12) are comparable to those in eqn (11); both equations contain terms related to VOC size (L or V_{mc}), VOC basicity and VOC acidity.

Hau and co-workers (53) adopt a rather different approach. They multiply values of NPT by K_w , the gas to water partition coefficient thus converting NPT into a biophase to water partition coefficient. Then $\text{NPT} \cdot K_w$ can be compared to a water to solvent partition coefficient such as the water to octanol partition coefficient, P_{oct} , as in eqn (13). The negative sign of the term in $\log P_{oct}$ arises because $\text{NPT} \cdot K_w$ refers to transfer from biophase to water and P_{oct} refers to transfer from water to octanol. The paucity of statistics for eqn (13) precludes any firm comparison with eqn (11) or eqn (12), but there is probably little difference in the three equations.

$$\text{Log}(\text{NPT} \cdot K_w) = 7.69 - 1.16 \log P_{oct} \quad (13)$$

$$N = 33, R^2 = 0.943$$

Subsequently, eqn (13) was used as a basis for estimating health guidelines, and it was suggested that threshold limit values (TLVs) of volatile organic compounds should not be more than 20% of a predicted NPT value (54).

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References

1. Parker GH. The relation of smell, taste and the common chemical sense in vertebrates. *J Acad Nat Sci Phila* 1912; 15: 221-234.
2. Keele CA. The common chemical sense and its receptors. *Arch Int Pharmacodyn Ther* 1962; 139: 547-557.
3. Bryant B, Silver WL. Chemesthesis: the common chemical senses. In Finger TE, Silver WL, Restrepo D., eds *The neurobiology of taste and smell*, 2nd ed., Wiley-Liss, New York, 2000: 73-100.
4. Ressler KJ, Sullivan SL, Buck LB. A molecular dissection of special patterning in the olfactory system. *Curr Opin Neurobiol* 1994; 4: 588-596.
5. Niimura Y, Nei M. Evolutionary dynamics of olfactory and other chemosensory receptor genes in vertebrates. *J Hum Genet* 2006; 51:505-17.
6. Firestein S. Olfaction: scents and sensibility. *Curr Biol* 1996; 6: 666-667.
7. Mori K, Yoshihara Y. Molecular recognition and olfactory processing in the mammalian olfactory system. *Prog Neurobiol* 1995; 45: 585-619.
8. Cometto-Muñiz JE, Cain WS. Thresholds for odor and nasal pungency. *Physiol Behav* 1990; 48: 719-725.
9. Cometto-Muñiz JE, Cain WS. Trigeminal and olfactory sensitivity: comparison of modalities and methods of measurement. *Int Arch Occup Environ Health* 1998; 71: 105-110.

10. Kobal G, Van Toller S, Hummel T. Is there directional smelling? *Experimentia* 1989; 45: 130-132.
11. Silver WL, Mason JR, Marshall DA, Maruniak JA. Rat trigeminal olfactory and taste responses after capsaicin desensitization. *Brain Res* 1985; 333: 45-54.
12. Cometto-Muñiz JE, Cain WS. Perception of odor and nasal pungency from a homologous series of volatile organic compounds. *Indoor Air* 1994; 4: 140-145.
13. Cometto-Muñiz JE, Cain WS, Abraham MH. Nasal pungency and odor of homologous aldehydes and carboxylic acids. *Exp Brain Res* 1998; 118: 180-188.
14. Abraham MH, Kumarsingh R, Cometto-Muñiz JE, Cain WS. Draize eye scores and eye irritation thresholds in man can be combined into one quantitative structure-activity relationship. *Toxicol in Vitro* 1998; 12: 403-408.
15. Cauna NK, Hinderer K, Wentges RT. Sensory receptor organs of the human nasal respiratory mucosa. *Am J Anat* 1969; 124: 187-210.
16. Finger TE, St Jeor V, Kinnamon JC, Silver WL. Ultrastructure of substance P- and CGRP-immunoreactive nerve fibres in the nasal epithelium of rodents. *J Comp Neurol* 1990; 294: 293-305.
17. Nielsen GD. Mechanisms of activation of the sensory irritant receptor by airborne chemicals. *Crit Rev Toxicol* 1991; 21: 183-208.
18. Alarie Y, Schaper M, Nielsen GD, Abraham MH. Structure-activity relationships of volatile organic chemicals as sensory irritants. *Arch Toxicol* 1998; 72: 125-140.
19. Cesare P, McNaughton P. Peripheral pain mechanisms. *Curr Opin Neurobiol* 1997; 7: 493-499.
20. McCleskey EW, Gold MS. Ion channels of nociception. *Ann Rev Physiol* 1999; 61: 835-856.

21. Eccles R, Jawad MS, Morris S. The effects of oral administration of (-) menthol on nasal resistance to airflow and nasal sensation of airflow in subjects suffering from nasal congestion associated with the common cold. *J Pharm Pharmacol* 1990; 42: 652-654.
22. Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence for neurogenic inflammation and its prevention by denervation and by pre-treatment with capsaicin. *Br J Pharmacol Chemother* 1967; 31: 138-151.
23. Alimohammadi H, Silver WL. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. *Chem Senses* 2000; 25: 61-66.
24. Inoue T, Bryant BP. Multiple types of sensory neurons respond to irritating volatile organic compounds (VOCs): calcium fluorimetry of trigeminal ganglion neurons. *Pain* 2005; 117: 193-203.
25. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjork HE. Specific C-receptors for itch in human skin. *J Neurosci* 1997; 17: 8003-8008.
26. Jord SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Hogestatt ED, Meng ID, Julius D. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature* 2004; 427: 260-265.
27. Barrow C, Alarie Y, Warrick J, Stock M. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. *Arch Environ Health* 1977; 32: 68-76.
28. Alarie Y, Kane L, Barrow C. Sensory irritation: the use of an animal model to establish acceptable exposure to airborne chemical irritants. In: Reeves AL, ed. *Toxicology: principles and practice, Volume 1*. New York: John Wiley and Sons; 1980: 48-92.

29. American Society for testing and materials (ASTM). Standard test method for estimating sensory irritancy of airborne chemicals. Designation E 981-84. Philadelphia, Pa. ASTM 1984.
30. Alarie Y. Bioassay for evaluating the potency of airborne sensory irritants and predicting acceptable levels of exposure in man. *Food Cosmet Toxicol* 1981; 19: 623-626.
31. Alarie Y. Dose-response analysis in animal studies: prediction of human responses. *Environ Health Perspect* 1981; 42: 9-13.
32. Nielsen GD, Alarie Y. Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkyl benzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. *Toxicol Appl Pharmacol* 1982; 65: 459-477.
33. Nielsen GD, Wolkoff P, Alarie Y. Sensory irritation: risk assessment approaches. *Regul Toxicol Pharmacol* 2007; 48: 6-18.
34. Kuwabara Y, Alexeeff GV, Broadwin R, Salmon AG. Evaluation and application of the RD₅₀ for determining acceptable exposure levels of airborne sensory irritants for the general public. *Environ Health Perspect* 2007; 115: 1609-1616.
35. Ferguson J. Use of chemical potentials as indexes of toxicity. *Proc Roy Soc (London)* 1939; B127: 387-404.
36. Brink F, Pasternak JM. Thermodynamic analysis of the effectiveness of narcotics. *J Cell Comp Physiol* 1948; 32: 211-233.
37. 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.

38. Muller J, Gref G. Recherche de relations entre toxicite de molecules d'interet industriel et proprietes physico-chimiques: test d'irritation des voies aeriennes superieures appliqué a quatre familles chimiques. *Fd Chem Toxic* 1984; 22: 661-664.
39. Roberts DW. QSAR for upper-respiratory tract irritation. *Chem-Biol Interactions* 1986; 57: 325-345.
40. 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.
41. Alarie Y, Schaper M, Nielsen GD, Abraham MH. Estimating the sensory irritating potency of airborne nonreactive volatile organic chemicals and their mixtures. *SAR and QSAR in Environ Res* 1996; 5: 151-165.
42. Abraham MH, Acree, Jr. WE, Mintz C, Payne S. Effect of anesthetic structure on inhalation anesthesia: implications for the mechanism. *J Pharm Sci* 2008; 97: 2373-2384.
43. Alarie Y, Nielsen GD, Andonian-Haftvan J, Abraham MH. Physicochemical properties of nonreactive volatile organic compounds to estimate RD₅₀: alternatives to animal studies. *Toxicol Appl Pharmacol* 1995; 134: 92-99.
44. Nielsen GD, Thomsen ES, Alarie Y. Sensory irritation receptor compartment properties. *Acta Pharm Nord* 1990; 1: 31-44.
45. Gagnaire F, Azim S, Simon P, Cossec B, Bonnet P, De Ceaurriz J. Sensory and pulmomary irritation of aliphatic amines in mice: a structure-activity relationship. *J Appl Toxicol* 1993; 13: 129-135.
46. Abraham MH, Whiting GS, Alarie Y, Morris JJ, Taylor PJ, Doherty RM, Taft RW, Nielsen GD. Hydrogen bonding.12. A new QSAR for upper respiratory tract irritation by airborne chemicals in mice. *Quant Struct-Act Relat* 1990; 9: 6-10.
47. Abraham MH, Ibrahim A, Zissimos AM. The determination of sets of solute descriptors from chromatographic measurements. *J Chromatogr A* 2004; 1037: 29-47.
48. Luan F, ma W, Zhang X, Zhang H, Liu M, Hu Z, Fan BT. Quantitative structure-activity relationship models for prediction of sensory irritants (log RD₅₀) of volatile organic compounds. *Chemosphere* 2006; 63: 1142-1153.

49. Abraham MH, Andonian-Haftvan J, Cometto-Muñiz JE, Cain WS. An analysis of nasal irritation thresholds using a new solvation equation. *Fund App Toxicol* 1996; 31: 71-76
50. Hawkins DM. The problem of overfitting. *J Chem Inf Comput Sci* 2004; 44: 1-12.
51. Abraham MH, Acree Jr. WE, Leo AJ, Hoekman D. Partition from water and from air into wet and dry ketones. *New J Chem* 2009; ...in press DOI: [10.1039/b813581a](https://doi.org/10.1039/b813581a)
52. Famini GR, Aguiar D, Payne MA, Rodriquez R, Wilson LY. (2002) Using the theoretical linear solvation energy relationship to correlate and predict nasal pungency thresholds. *J Mol Graphics Model* 2002; 20: 277-280.
53. Hau KM, Connell DW, Richardson BJ. Quantitative structure-activity relationship for nasal pungency thresholds of volatile organic compounds. *Toxicol Sci* 1999; 47: 91-98.
54. Hau KM, Connell DW, Richardson BJ. Use of partition models in setting health guidelines for volatile organic compounds. *Regul Toxicol Pharmacol* 2000; 31: 22-29.

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