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An Analysis of Nasal Irritation Thresholds Using a New Solvation Equation

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An Analysis of Nasal Irritation Thresholds Using a New Solvation Equation. ABRAHAM, M. H., ANDONIAN-HAFTVAN, J., COMETTO-MUÑIZ, J. E., AND CAIN, W. S. (1995) *Fundam. Appl. Toxicol.*

Abstract

In the present paper we have developed a quantitative structure–activity relationship (QSAR) equation for nasal pungency caused by nonreactive volatile organic compounds (VOCs). Our QSAR was developed upon previously published nasal pungency thresholds in anosmics, i.e., patients lacking a sense of smell and thus responding only to sensory irritation evoked by trigeminal nerve stimulation. The reported solvation equation, which fits the data with considerable precision, describes sensory potency in terms of interaction via electron pairs, dipolarity/polarizability, hydrogen bond acidity and basicity, and hydrophobicity. It correspondingly suggests relevant physicochemical properties of the biophase where the sensory response is brought about. The equation implies that in the range of molecular size where nonreactive VOCs can produce any pungency, transport from the air to the biophase strictly determines potency. In this respect, the potency of nasal pungency shares characteristics with the ability of VOCs to cause narcosis and anesthesia.

Introduction

The presence of airborne chemicals known as volatile organic compounds (VOCs) in the environment, including the home and the workplace, can lead to sensory irritation of the upper airways, a widely cited health effect from polluted indoor air (Cometto-Muñiz and Cain, 1992; Mølhave, 1992). About half the threshold limit values (TLVs) (ACGIH, 1991) set by the American Conference of Governmental Industrial Hygienists (ACGIH) are based on sensory irritation (Alarie, 1981). Direct studies in humans are necessarily restricted to the less toxic VOCs. In this class there are available only about forty experimentally derived values of nasal pungency (irritation) thresholds obtained with uniform methodology (Cometto-Muñiz and Cain, 1990, 1991, 1993, 1994). Of additional pungency thresholds found in the occupational literature (Ruth, 1986) no two were obtained under uniform methodology and exposure conditions.

The number of VOCs that can be encountered at home or in the workplace is enormous. The number of industrial chemicals exceeds 100,000, of which perhaps one third (30,000) could be classified as volatile organic compounds. The recent comprehensive survey of Schaper (1993) contains results on upper respiratory tract irritation in mice for only 244 VOCs. It is clearly uneconomic to obtain sensory irritation data either directly on humans or indirectly from an animal assay for more than a very small proportion of VOCs that could be encountered in everyday life.

The aim of the present work is to devise quantitative structure–activity relationships (QSARs) that could be used to correlate nasal pungency thresholds, as determined by Cometto–Muñiz and Cain (1990, 1991, 1993, 1994), with relevant physicochemical properties and thereby to approach prediction of such thresholds.

The intentional selection of relatively nonreactive chemicals for this investigation rested on: 1) the importance of obtaining sensory responses from human volunteers who may not be safely exposed to reactive compounds, 2) an interest in learning about sensory irritation from substances that are not simply directly corrosive and destructive to tissue, and 3) the knowledge that sensory irritation of mucous membranes emerges as a relevant symptom in virtually all cases of complaints about poor indoor air quality (see Cometto–Muñiz and Cain, 1992) yet, invariably, chemical analysis of the spaces reveals exclusively VOCs of the relatively nonreactive type (Saarela et al., 1993). A calculation of nasal pungency threshold for a reactive VOC could, in addition, provide an estimate of the minimum potency for a substance with its particular physicochemical properties: this could then be used as a "base–line" for further analysis.

Methods

In the present paper, equation (1) (see Appendix) was applied to nasal pungency thresholds obtained from the literature (Cometto–Muñiz and Cain, 1990, 1991, 1993, 1994). These published thresholds had two advantages: first, they were measured in subjects who were clinically diagnosed as anosmics, i.e., lacking a sense of smell, and, thus, unbiased by odor sensations. Second, they were obtained with a uniform methodology and procedure, which allows a

firm ground for developing a QSAR. Table 1 summarizes the results from the four studies used as the source for nasal pungency thresholds.

Insert Table 1 about here

Descriptors for the selected VOCs were either available from the literature (Abraham, 1993b) or calculated for the present work (Table 2). Testing homologous series, where physicochemical properties change systematically, aims at uncovering relationships between changes in such properties and changes in sensory potency. Many of the substances in Table 2 have been found in indoor air (Brown et al., 1994; Wolkoff and Wilkins, 1993).

Insert Table 2 about here

Having the nasal pungency thresholds, i.e., the term SP in equation (1), and values of the descriptors (R_2 , π_2^H , α_2^H , β_2^H , L^{16}) for every VOC, we employed the method of multiple linear regression analysis to obtain the constants c, r, s, a, b, and l (Massart et al., 1988). The resulting new equation is described in the results section. Each term in this equation was analyzed for significance using the t-test.

Results

Nasal pungency thresholds are denoted as NPT in units of ppm. These values appear in Table 2, as $\log 1/\text{NPT}$, together with their relevant descriptors. We use $1/\text{NPT}$ because the larger this quantity the more potent is the VOC. When equation (1) was applied to the set of 34 $\log 1/\text{NPT}$ values, the R_2

descriptor failed to show significance and was discarded. The remaining four descriptors yielded the equation:

$$\log 1/\text{NPT} = - 8.562 + 2.209 \pi_2^{\text{H}} + 3.417 \sum \alpha_2^{\text{H}} + 1.535 \sum \beta_2^{\text{H}} + 0.865 \log L^{16} \quad (2)$$

(±0.372) (±0.613) (±0.527) (±0.419) (±0.037)

$$n = 34 \quad r = 0.976 \quad \text{sd} = 0.27 \quad F = 144$$

Here, n is the number of data points (VOCs), r is the correlation coefficient, sd is the standard deviation in log 1/NPT, and F is the F-statistic. The standard deviation for each of the five coefficients is shown between brackets underneath the coefficients. The t-test showed all coefficients to be significant at or below p=0.001. Calculated log 1/NPT on equation (2) appear in Table 2, with a plot of observed versus calculated values in Figure 1.

Insert Figure 1 about here

Discussion

Equation (2) appears to be a good representation of the experimental NPT values and could be used as a first estimation of further values. One advantage of the general equation (1) is that in previous studies of gas-liquid chromatography, upper respiratory tract irritation in mice, inhibition of firefly luciferase enzyme by aqueous nonelectrolytes, and general anesthesia, among others, (Abraham 1993a, 1993b), it has been shown to apply irrespective of chemical functionality. Thus, for nonreactive VOCs, the equation should allow estimates of NPT values for chemical types not included among the training set

of compounds (Table 2). Of course, care should be taken to confine estimations to VOCs with descriptor values within the limits of the training set (or perhaps just outside), but even with this restriction it is possible to estimate NPT values for numerous VOCs. We plan to determine further nasal pungency thresholds in order to check the predictions of the present equation.

Interpretation of Processes. Equation (1) can be used to interpret factors involved in chemical or biological processes. The equation applies (Abraham, 1993a, 1993b) to what we can term 'transport' processes, those in which either the distribution of a solute between phases, or the rate of transfer of a solute from one phase to another, forms the key step. Equation (1) would not apply to VOCs that exerted their action through exact geometrical or conformational states because such changes in molecular structure would change the physical sorption properties of the chemical only slightly whereas, when relevant, stereochemical differences could change potency dramatically. The success of equation (1) in the correlation of the $\log 1/\text{NPT}$ values suggests that the key step involved is the transport of the VOC to the receptive biophase.

If pungent VOCs penetrate the nasal epithelium via partitioning into the plasma membranes of epithelial cells, they could act primarily in these cells which in turn could send signals to the nerve endings, or they could act directly on the plasma membrane of the endings themselves (see Cain and Cometto-Muñiz, 1995). The present approach does not resolve this issue since it is compatible with transport-based models having one stage or more than one (Abraham et al., 1994). Abraham, Nielsen, and Alarie (1994) have suggested three possible models for sensory irritation in mice that are transport driven,

and the present results indicate that the same models should apply to human nasal pungency as well.

The nasal tissues, both olfactory and respiratory, contain high amounts of numerous enzymes capable of metabolizing inhaled vapors (for a review see Dahl and Hadley, 1991). Among those enzymes, oxidoreductases, carboxylesterases, and cytochrome P-450 are likely to metabolize many of the VOCs shown in Table 2. The role of these enzymes in olfaction is largely unknown and subject to many possibilities (Lewis and Dahl, 1995). Their role in nasal pungency is also unknown. Could some of our pungency thresholds reflect a response to breakdown products? We cannot rule out this possibility but we deem it unlikely: If some important percentage of our stimuli were acting via metabolites — which most likely would have different descriptor values than the parent compound — our equation would not show the high correlation illustrated in Figure 1.

Ferguson Rule. One of the earliest attempts to relate biological potencies of gaseous compounds to a physicochemical property was that of Ferguson (1939), who suggested that anesthetic or narcotic potency was proportional to the saturated vapor pressure of the bulk liquid anesthetic. Brink and Posternak (1948) claimed some thermodynamic validity for Ferguson's principle. There are, however, marked exceptions to the rule (Cammarata, 1975). The principle is a useful first approximation for biological potency of unreactive gases and vapors within chemical series, but may fail unpredictably across series (Abraham et al., 1994).

We applied the Ferguson (1939) rule to the data in Table 2, where we give the VOC vapor pressure in atm at 298K, as $\log 1/P$ values. Application to the entire set of VOCs leads to:

$$\log 1/NPT = - 5.387 + 0.949 \log 1/P \quad (3)$$

$$n = 34 \quad r = 0.957 \quad sd = 0.34 \quad F = 351$$

The Ferguson equation (3) works well in this instance, see also Figure 2, and could be used to estimate $\log 1/NPT$ values. Nevertheless, in addition to its tendency to fail for structurally unrelated compounds (Kratz and Rudo, 1966) and despite its widespread use in the toxicological literature, there is little understanding of its chemical or physical basis. It has generally been used to indicate the existence of a state of equilibrium among the various phases of a multiphase system. Insofar as such a principle correlates with solubility of VOCs in the aqueous-lipid phase environment of the mucosal epithelium, then the two approaches should indeed correlate.

Insert Figure 2 about here

Our method, based on the general equation (1), has already been applied to retention data of organic compounds on a variety of gas-liquid chromatographic stationary phases (Abraham et al., 1991a; Abraham et al., 1991b; Abraham et al., 1991c; Abraham et al., 1993a; Poole and Kolli, 1993), and to the solubility of gases and vapors in solvents (Abraham et al., 1993b) and in biological phases (Abraham and Weathersby, 1994). An earlier version of equation (1) was used to analyze the effect of nonreactive VOCs on upper respiratory tract irritation of male Swiss OF1 mice (Abraham et al., 1990).

These applications were extremely successful, and serve to validate the general approach leading to equation (1). Additionally — in contrast to the Ferguson rule — our equation provides a quantitative description of particular physicochemical properties that seem to underlie the nasal pungency potency of a VOC, and accordingly of those complementary properties of the receptive biophase.

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Table 1. Average NPT ($\pm$ SD) in log ppm from the literature and used in the present study. All NPT were obtained from anosmics, via an ascending concentration series with a two-alternative, forced-choice procedure (details described in the original publications). NPTs were obtained with squeeze and sniff bottles (Cain, 1989) through short-term (about 2-sec) exposures.

Cometto-Muñiz and Cain (1990)¹

Stimulus	Average log NPT	SD
Methanol	4.530	0.115
Ethanol	3.908	0.018
Propanol	3.494	0.054
Butan-1-ol	3.199	0.139
Pentan-1-ol	3.205	0.064
Hexan-1-ol	2.621	0.155
Heptan-1-ol	2.322	0.021
Octan-1-ol	1.988	0.047
Pyridine	3.105	0.241

Cometto-Muñiz and Cain (1991)²

Stimulus	Average log NPT	SD
Methyl acetate	5.051	0.333
Ethyl acetate	4.828	0.151
n-Propyl acetate	4.245	0.288
n-Butyl acetate	3.562	0.268
n-Pentyl acetate	3.217	0.173
n-Hexyl acetate	2.803	0.360
n-Heptyl acetate	2.492	0.287
n-Octyl acetate	1.954	0.000
n-Decyl acetate	0.699	0.000
n-Dodecyl acetate	0.097	0.000

Cometto-Muñiz and Cain (1993)³

Stimulus	Average log NPT	SD
Propanone	5.116	0.186
Pentan-2-one	3.472	0.150
Heptan-2-one	2.906*	0.334
Nonan-2-one	2.530	0.147
Propan-2-ol	4.259	0.243
Butan-2-ol	3.975	0.182
t-Butanol	4.516	0.136
Heptan-4-ol	2.525	0.091
s-Butyl acetate	3.597*	0.391
t-Butyl acetate	3.976*	0.557

Cometto-Muñiz and Cain (1994)⁴

Stimulus	Average log NPT	SD
Toluene	4.471	0.055
Ethylbenzene	4.004	0.087
n-Propylbenzene	3.172	0.082
Chlorobenzene	4.023	0.058
Oct-1-yne	4.486	0.016

1 Three anosmics tested: one male (39 year-old, nonsmoker, congenital anosmic) and two females (a 35 year-old, nonsmoker, head-trauma anosmic, and a 20 year-old, smoker, congenital anosmic).

2 Four anosmics tested: two males (a 40 year-old, nonsmoker, congenital anosmic, and a 64 year-old, previous smoker, head-trauma anosmic) and two females (a 35 year-old, nonsmoker, head-trauma anosmic, and a 59 year-old, nonsmoker, congenital anosmic).

3 Four anosmics tested: three males (a 41 year-old, nonsmoker, congenital anosmic, a 50 year-old, previous smoker, head-trauma anosmic, and a 65 year-old, previous smoker, head-trauma anosmic) and one female (a 60 year-old, nonsmoker, congenital anosmic).

4 Four anosmics tested: two males (a 42 year-old, nonsmoker, congenital anosmic, and a 65 year-old, previous smoker, head-trauma anosmic) and two females (a 61 year-old, nonsmoker, congenital anosmic, and a 67 year-old, smoker, head-trauma anosmic).

* Values originally reported as 2.448, 2.859, and 3.325 for heptan-2-one, s-butyl acetate, and t-butyl acetate, respectively. In the present paper these values were re-calculated based on more reliable sources of vapor pressure than the single sources used originally.

Table 2. Descriptors and values of log 1/NPT used in the calculations^a

Compound	π_2^H	$\sum \alpha_2^H$	$\sum \beta_2^H$	log L ¹⁶	log 1/P	log 1/NPT	
						obs	calc ^b
Methanol	0.44	0.43	0.47	0.970	0.78	-4.53	-4.56
Ethanol	0.42	0.37	0.48	1.485	1.11	-3.91	-4.35
Propan-1-ol	0.42	0.37	0.48	2.031	1.58	-3.49	-3.88
Propan-2-ol	0.36	0.33	0.56	1.764	1.24	-4.26	-4.25
Butan-1-ol	0.42	0.37	0.48	2.601	2.05	-3.20	-3.38
Butan-2-ol	0.36	0.33	0.56	2.338	1.64	-3.76	-3.76
t-Butanol	0.30	0.31	0.60	1.963	1.26	-4.52	-4.22
Pentan-1-ol	0.42	0.37	0.48	3.106	2.55	-3.21	-2.94
Hexan-1-ol	0.42	0.37	0.48	3.610	3.02	-2.62	-2.51
Heptan-1-ol	0.42	0.37	0.48	4.115	3.51	-2.32	-2.07
Heptan-4-ol	0.36	0.33	0.56	3.850	2.90	-2.53	-2.45
Octan-1-ol	0.42	0.37	0.48	4.619	3.97	-1.99	-1.64
Pyridine	0.84	0.00	0.52	3.022	1.57	-3.11	-3.29
Methyl acetate	0.64	0.00	0.45	1.911	0.55	-5.05	-4.80
Ethyl acetate	0.62	0.00	0.45	2.314	0.91	-4.83	-4.50
n-Propyl acetate	0.60	0.00	0.45	2.819	1.35	-4.24	-4.11
n-Butyl acetate	0.60	0.00	0.45	3.353	1.84	-3.56	-3.64
s-Butyl acetate	0.57	0.00	0.47	3.054	1.52	-3.60	-3.94
t-Butyl acetate	0.54	0.00	0.47	2.802	1.28	-3.98	-4.22
n-Pentyl acetate	0.60	0.00	0.45	3.844	2.27	-3.22	-3.22
n-Hexyl acetate	0.60	0.00	0.45	4.351	2.74	-2.80	-2.78
n-Heptyl acetate	0.60	0.00	0.45	4.865	3.19	-2.49	-2.34
n-Octyl acetate	0.60	0.00	0.45	5.364	3.65	-1.95	-1.90
n-Decyl acetate	0.60	0.00	0.45	6.373	4.57	-0.70	-1.03
n-Dodecyl acetate	0.60	0.00	0.45	7.381	5.48	-0.10	-0.16
Propanone	0.70	0.04	0.49	1.696	0.52	-5.12	-4.66
Pentan-2-one	0.68	0.00	0.51	2.755	1.33	-3.47	-3.89
Heptan-2-one	0.68	0.00	0.51	3.760	2.30	-2.91	-3.02
Nonan-2-one	0.68	0.00	0.51	4.735	3.18	-2.53	-2.18
Toluene	0.52	0.00	0.14	3.325	1.43	-4.47	-4.32
Ethylbenzene	0.51	0.00	0.15	3.778	1.90	-4.00	-3.94
n-Propylbenzene	0.50	0.00	0.15	4.230	2.35	-3.17	-3.57
Chlorobenzene	0.65	0.00	0.07	3.657	1.80	-4.02	-3.85
Oct-1-yne	0.23	0.12	0.10	3.521	1.75	-4.49	-4.44

^a Descriptor values from Abraham, 1993b — except for s-butyl acetate and t-butyl acetate (from this work) — and observed values of log 1/NPT from Cometto-Muñiz and Cain, 1990, 1991, 1993, 1994.

^b On equation 2.

Figure Legends

Figure 1. Observed vs. calculated values for $\log 1/\text{NPT}$ from equation (2). NPT refers to nasal pungency thresholds (in ppm) from Cometto-Muñiz and Cain, 1990, 1991, 1993, 1994.

Figure 2. Observed vs. calculated values for $\log 1/\text{NPT}$ from the Ferguson principle — equation (3) — (see text).

FIGURE 1

FIGURE 2

Appendix

The present approach is based on the general solvation equation of Abraham (1993a, 1993b):

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

SP is a property of a series of solutes, or VOCs. In the present case, SP will be the reciprocal of the nasal pungency threshold in ppm, denoted as 1/NPT. Descriptors of the compounds are as follows (Abraham, 1993a, 1993b): R_2 is an excess molar refraction that can be determined simply from knowledge of the refractive index of the compound, π_2^H is the dipolarity/polarizability of the VOC, $\sum \alpha_2^H$ is the overall or effective hydrogen-bond acidity of the VOC, and $\sum \beta_2^H$ is the overall or effective hydrogen-bond basicity of the VOC. L^{16} is the gas-liquid partition coefficient of the VOC on hexadecane at 298K (Abraham et al., 1987). If values of SP are known for a series of VOCs for which descriptors are available, equation (1) can be solved by the method of multiple linear regression analysis, MLRA, to yield the constants c, r, s, a, b and l. Not every term in equation (1) may be significant, and each term is analyzed using Student's t-test (Chatterjee and Price, 1977). Usually, a term is retained only if the t-test shows that it accounts for a significant proportion of the variance ($p \leq 0.05$).

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