Published in final edited form as:
Toxicol In Vitro. 2010 March ; 24(2): 357–362. doi:10.1016/j.tiv.2009.11.009.

The Biological and Toxicological Activity of Gases and Vapors

Michael H Abraham[1], **Ricardo Sánchez-Moreno**[1], **Javier Gil-Lostes**[1], **William E. Acree Jr.**[2], **J. Enrique Cometto-Muñiz**[3], and **William S. Cain**[3]

[1] Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, UK

[2] Department of Chemistry, 1155 Union Circle #305070, University of North Texas, Denton, TX 76203-5017, U.S.A

[3] Chemosensory Perception, Laboratory, Department of Surgery (Otolaryngology), University of California, San Diego, La Jolla, CA 92093-0957, USA

Abstract

A large amount of data on the biological and toxicological activity of gases and vapors has been collected from the literature. Processes include sensory irritation thresholds, the Alarie mouse test, inhalation anesthesia, etc. It is shown that a single equation using only five descriptors (properties of the gases and vapors) plus a set of indicator variables for the given processes can correlate 643 biological and non-lethal toxicological activities of 'non-reactive' compounds with a standard deviation of 0.36 log unit. The equation is scaled to sensory irritation thresholds obtained by the procedure of Cometto-Muñiz, and Cain, and provides a general equation for the prediction of sensory irritation thresholds in man. It is suggested that differences in biological/toxicological activity arise primarily from transport from the gas phase to a receptor phase or area, except for odor detection thresholds where interaction with a receptor(s) is important.

INTRODUCTION

The toxicological and biological activities of gases and vapors includes such processes as upper respiratory tract irritation in mice (Alarie, 1966, 1973), inhalation anesthesia in mice (Davies *et al*., 1974, 1976) and in rats (Won *et al*., 2006), convulsant activity in rats (Eger *et al*., 1999), and eye irritation thresholds, nasal pungency thresholds and odor detection thresholds in man (see reviews in Cometto-Muñiz, 2001, Cometto-Muñiz et al., 2004). Because of the importance of these effects, there have been numerous attempts to obtain equations that correlate these activities and which can be used to predict further values of the activity (Abraham *et al*., 1990, 1998a, 1998b, 2002, 2007, 2008a; Abraham and Acree 2009; Alarie *et al*., 1995 and 1996; Davies *et al*., 1974, 1976; Famini *et al*., 2002; Hau and Connell 1998, Hau *et al*., 1999; Luan *et al*., 2006; Muller and Gref 1984; Roberts 1986; Sewell and Sear, 2004 and 2006).

In any equation that is established, predictions should only be made for volatile compounds, VCs, that lie within the chemical space of the VCs used to construct the equation. The problem with all the equations so far established is that the VCs used to construct the equations are too small in number and too close in variety to provide predictions for a wide range of VCs. For example, quantitative structure-activity relationships (QSARs) have been derived for nasal pungency thresholds (NPTs) using 33 VCs (Hau *et al*., 1999) or 44 VCs (Abraham *et al*., 1998b; Famini *et al*., 2002), all of which are rather simple molecules. The set of 33 or 44 compounds includes no ethers, no fluorocompounds, no bromocompounds, no nitriles, no

Correspondence to: Michael H Abraham.

nitrocompounds, and only one heterocyclic compound (pyridine) so that predictions are severely limited to a few specific types of VC. It is the aim of the present work to ascertain if it is possible to combine several different biological and non-lethal toxicological processes in the same equation, and thus to extend the chemical space of the VCs and the area of possible predictions. Of course, the statistics of any combined equation will not be expected to be as good as those for the separate equations, but the hope is that any combined equation will still be good enough to yield reasonable predictions of biological/toxicological activity of gases and vapors. Note that we use the term 'volatile compounds' rather than 'volatile organic compounds' because we deal with inorganic compounds as well as organic compounds.

MATERIALS AND METHODS

The methods we use are based on two linear free energy relationships, LFERs, equation [1] and equation [2]

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

$$\boldsymbol{Y}=c+e\cdot\mathbf{E}+s\cdot\mathbf{S}+a\cdot\mathbf{A}+b\cdot\mathbf{B}+v\cdot\mathbf{V} \quad (2)$$

The dependent variable, **Y**, is some property of a series of solutes in a given fixed process. For example **Y** might be log (1/NPT) for a series of VCs. The five independent variables, or descriptors, are properties of the VCs as follows (Abraham, 1993; Abraham *et al*., 2004). **E** is the VC excess molar refraction and reflects the ability of the solute to undergo general dispersion interactions, **S** is the VC dipolarity (plus some polarizability), **A** is the VC hydrogen bond acidity, **B** is the VC hydrogen bond basicity, **L** is the solubility of the gaseous VC in hexadecane at 25°C, expressed as the gas to hexadecane partition coefficient, and **V** is the McGowan characteristic volume. **L** and **V** can be regarded as measures of the size of the VC. The regression coefficients, c, e, s, a, b, l, and v are obtained by multiple linear regression analysis.

Equations on the lines of equation [1] have previously been obtained for eye irritation thresholds (Abraham *et al*., 1998a), nasal irritation (pungency) thresholds (Abraham *et al*., 1998b), odor detection thresholds (Abraham *et al*., 2002), upper respiratory irritation in mice (Abraham *et al*., 1990), inhalation anesthesia (Abraham *et al*., 2008a) and convulsant activity (Abraham and Acree, 2009). In the case of convulsant activity, four compounds were more potent than predicted (Eger *et al*., 1999) from solubility in olive oil (perfluorodimethylcyclobutane, 1,1,1,2,2,3,3,4,5,6,6,6-dodecafluorohexane, bis(2,2,2-trifluoroethyl)ether, and perfluorotoluene). In addition, scores in the Draize rabbit eye test for pure liquids can be converted into scores for the corresponding vapors by the liquid saturated vapor pressure (Abraham *et al*., 1998a, 1998c). We have included a few VCs for which Draize scores have subsequently been recorded (Takahashi *et al*., 2008). Concentrations for aqueous tadpole narcosis (Bowen *et al*., 2006) have been converted into gaseous concentrations by use of the gas to water partition coefficient (Abraham and Acree, 2007); values of log(1/C), where C is the gaseous narcotic concentration, were used as the function of activity. Only data for the species *Rana temporaria* were used. We could have included data for other tadpole species, but that would have meant another indicator variable for each species, and a more complicated general equation than was necessary.

The data used in the above studies, together with more recent data on upper respiratory irritation in mice (Alarie *et al*., 1995 and 1996; Nielsen *et al*., 2007), as log (RD_{50}) can all be collected

together. RD_{50} is the vapor concentration of a VC in ppm that reduces the rate of breathing of a mouse by 50%. For nasal pungency thresholds, eye irritation thresholds and odor detection thresholds we use log(1/NPT), log(1/EIT) and log(1/ODT), in units of ppm, so that the larger the numerical value, the more potent is the VC. In the case of inhalation anesthesia in mice (Davies *et al*., 1974, 1976) further studies at the same organization were later carried out (Bagnall *et al*., 1977, 1978, 1979a, 1979b, 1979c). However, we have not been able to include these results at all; possibly a different protocol was used in the later studies. We use the original units, rather than converting them all into some common unit, in order to make it easier to check the original data, and in order to make predictions without the necessity of converting units. In any case, all the units used are molar quantities as required (Dearden *et al*., 2009). The units of RD_{50}, NPT, EIT and ODT are ppm (vol/vol) so that by Avogadro's hypothesis, these all correspond to mol/volume. The units of inhalation anesthesia and convulsions are partial pressure, but since PV = RT it follows that log P is proportional to −log V, and, again by Avogadro's hypothesis, this is (the logarithm of) a molar quantity. The end point for inhalation anesthesia in mice (Davies *et al*., 1974, 1976) was given as vol/vol, so again is a molar quantity. Hence all the data we have used are molar quantities.

We were able to collect 720 numerical values for the biological activity of VCs, see Supplementary material. Of course, this is not 720 compounds, because many compounds have more than one entry.

In order that the activity of compounds in two processes can be put on the same scale, it is necessary that there be a constant difference between the activity of corresponding compounds in the two processes. Then this constant difference can be modeled by incorporation of an indicator variable in a general equation. We use equation (1) because that has been the basis for analyses of several measures of biological/toxicological activity, and we choose eye irritation as a 'standard', because it is one of the few processes that refer directly to effects on humans, and because we are particularly interested in sensory irritation – the combination of eye irritation and nasal pungency. Then for any other process, an indicator variable is added to equation (1). If several other processes are included, an indicator variable is needed for each process.

RESULTS

All the data we use is given in the Supplementary Table, together with the VC descriptors used in the calculations. These descriptors have all been obtained from experimental data, as explained before (Abraham *et al*., 2004). We first show how the present method leads to an equation that includes VCs that cover a very large chemical space. The chemical space of a set of VCs can be represented by the descriptors in equation (1) – the larger the numerical variation in the descriptors the larger is the chemical space. If the five descriptors were plotted as points in five-dimensional space, the volume enclosed by the points would be an exact measure of the chemical space. In order to visualize the chemical space, we use principal components analysis, PCA, transform the five columns of descriptor data into five principal components or PCs. The scores for the first two principal components typically contain about 80% of the total information. Then a plot of PC2 against PC1 for a given process will give an indication of the chemical space of the VCs used in that process.

In Fig. 1 is given a plot of PC2 against PC1 for eye irritation thresholds (Abraham *et al*., 1998a), and for inhalation anesthesia (Davies *et al*., 1974,1976). The chemical space covered by the two sets of VCs is completely different, and so if it were possible to combine the data, the resulting equation would cover a much wider chemical space than either set separately, and would be much more general.

For the analysis of the 720 data points listed in the Supplementary material, all were first included in the regression, and outliers then removed. Our criterion for an outlier was that it deviated by more than 2.8 standard deviations of the regression equation. This criterion was not chosen arbitrarily, but was selected so that we did not remove any VCs in the mouse assay test listed as operating through a physical mechanism (Alarie *et al*., 1995 and 1996; Nielsen *et al*., 2007); these workers classed VCs into those operating through a physical mechanism and those operating through a chemical mechanism. There were 53 outliers out of 147 VCs in the mouse assay test. These included VCs such as the isocyanates with a very reactive carbonyl group, and α,β-unsaturated compounds known to react with nucleophiles through Michael-type addition reactions (Yarbrough and Schultz 2007; Schultz *et al*., 2007).

As regards odor detection thresholds, ODTs, the terms ‘physical’ or ‘chemical’ are not very useful. In an analysis of ODTs, it was found (Abraham *et al*., 2007) that a compound such as octan-1-ol was an outlier, although it cannot be regarded as acting through a ‘chemical’ mechanism. It was suggested that the terms ‘selective’ and ‘specific’ were more appropriate. A selective process is one in which small structural changes in the VC evoke predictable and rather small changes in biological activity, and a specific process is one in which small structural changes in the VC may evoke less predictable and often large changes in biological activity (Abraham *et al*., 2007). The factors that lead to a specific process have not fully been elucidated, although it has been found that a particular maximum unfolded length of about 12 Å leads to enhanced potency (Abraham *et al*., 2002). Of the 64 compounds for which we had ODT values, 20 were outliers. It is known that statistically reasonable equations for log (1/ODT) can only be set up if quite a large number of VCs are omitted (Abraham *et al*., 2007) and so it is no surprise that there are outliers in the ODT set.

The only other outliers were pentane, urea, nicotine and strychnine in the calculated inhalation anesthesia of tadpoles (Abraham and Acree, 2007); urea and nicotine were outliers in the regression equation for aqueous anesthesia of tadpoles (Bowen *et al*., 2006). A summary of the number of VCs in the various processes is in Table 1, and full details are in the Supplementary Table.

Application of equation [1] plus the indicator variables shown in Table 1 to the 720 data points led to equation [3], after deletion of the 77 outliers.

$$\begin{aligned} \boldsymbol{Y} = &-7.805 + 0.056\,\mathbf{E} + 1.587\,\mathbf{S} + 3.431\,\mathbf{A} + 1.440\,\mathbf{B} + 0.754\mathbf{L} + 0.553\,\mathbf{Idr} + \\ &2.777\,\mathbf{Iodt} - 0.036\,\mathbf{Inpt} + 6.923\,\mathbf{Imac} + 0.440\,\mathbf{Ird50} + 8.161\,\mathbf{Itad} + 7.437\,\mathbf{Icon} + \\ &4.959\,\mathbf{Idav} \\ N=643,\ &\mathrm{SD}=0.357,\ r^2=0.992,\ q^2=0.992,\ \mathrm{PRESS}=84.536,\ F=6083,\ \mathrm{PSD}=0.367 \end{aligned} \tag{3}$$

Here, N is the number of data points, SD is the regression standard deviation, r is the correlation coefficient, q and PRESS are the leave-one-out statistics, F is the F-statistic and PSD is the ‘predictive standard deviation’ (Hawkins, 2004; Abraham *et al*., 2009) PDS is defined similarly to SD; the latter is given by $\mathrm{SD} = \sqrt{[\mathrm{SSE}/(N - 1 - v)]}$ where SSE is the sum of squares of errors and v is the number of independent variables, and $\mathrm{PSD} = \sqrt{[\mathrm{PRESS}/(N - 1 - v)]}$. PSD is a very useful statistic and can be taken as a measure of the predictive capability of the equation. It can be seen that the coefficient of the NPT indicator variable is very small (−0.036) so that NPT and EIT values are almost exactly matched and the NPT indicator variable can be removed. The e-coefficient (0.056) is not statistically significant and if this is removed as well, equation [4] results. The r^2 statistic of 0.992 indicates that over 99% of the variance in the data is accounted for. This will include random experimental and biological error, but not, of course, systematic error.

$$\boldsymbol{Y} = -7.839 + 1.620\,\mathbf{S} + 3.431\,\mathbf{A} + 1.413\,\mathbf{B} + 0.759\,\mathbf{L} + 0.578\,\mathbf{Idr} + 2.801\,\mathbf{Iodt} + 6.941\,\mathbf{Imac} + 0.465\,\mathbf{Ird50} + 8.190\,\mathbf{Itad} + 7.452\,\mathbf{Icon} + 4.972\,\mathbf{Idav}$$

$$N=643,\ \mathrm{SD}=0.357,\ r^2=0.992,\ q^2=0.992,\ \mathrm{PRESS}=83.998,\ F=7199,\ \mathrm{PSD}=0.365 \quad (4)$$

The F-statistic is often used as a criterion for removing descriptors; the larger the F-statistic the more efficient is the equation. A more powerful method is through the Akaike information criterion, AIC, (Cavanaugh, 1997) which takes into account the number of descriptors, *p*, the number of data points, *N*, and the regression residual sum of squares, RSS, also known as SSE, the error sum of squares,

$$\mathrm{AIC} = 2p + N[\ln(2^*\pi^*\mathrm{RSS}/N) + 1] \quad (5)$$

The smaller the value of AIC, the more efficient or economic is the model. Note that equation [5] can only be applied to a set of equations with the same number of data points. We give in Table 2 details of the application of the AIC criterion to equation [3] as we remove successively the least important descriptor. There is little improvement in efficiency if the descriptors **Inpt** and **E** are removed, but removal of the next least important descriptor, **Ird50**, leads to a very considerable increase in AIC. The AIC criterion marks equation [4] as the most efficient (as does the F-statistic). Very little can be deduced from the values of r^2 or SD.

The statistics of equation [4] are practically identical to those of equation [3] and so can be used for the prediction of sensory irritation thresholds (SIT) in humans. In this case, all the other indicator variables can be set to zero to leave equation [6] as the most soundly-based equation for the prediction of sensory irritation thresholds in humans, as log(1/SIT), with an estimated predictive error of 0.36 log units.

$$\boldsymbol{Y} = -7.839 + 1.620\,\mathbf{S} + 3.431\,\mathbf{A} + 1.413\,\mathbf{B} + 0.759\,\mathbf{L} \quad (6)$$

We also investigated the use of equation [2] in the analysis of activity. Although equation [1] is usually better than equation [2] for the correlation and prediction of processes involving transfer of gases to a condensed phase, equation [2] has an advantage that the descriptor **V** can be calculated from structure. Thus in cases where the **L** descriptor cannot be obtained, equations [7] and [8] can be used to predict sensory irritation thresholds with little loss in predictive capability (PSD = 0.40 log units). In equation [7] isostearyl alcohol was an additional outlier in the EIT from Draize scores data set.

$$\boldsymbol{Y} = -8.538 + 1.098\,\mathbf{E} + 2.174\,\mathbf{S} + 3.707\,\mathbf{A} + 1.459\,\mathbf{B} + 2.663\,\mathbf{V} + 0.621\,\mathbf{Idr} + 2.820\,\mathbf{Iodt} + 6.936\,\mathbf{Imac} + 0.469\,\mathbf{Ird50} + 8.220\,\mathbf{Itad} + 7.437\,\mathbf{Icon} + 5.051\,\mathbf{Idav}$$

$$N=642,\ \mathrm{SD}=0.391,\ r^2=0.991,\ q^2=0.990,\ \mathrm{PRESS}=100.588,\ F=5503,\ \mathrm{PSD}=0.400 \quad (7)$$

$$\boldsymbol{Y} = -8.538 + 1.098\,\mathbf{E} + 2.174\,\mathbf{S} + 3.707\,\mathbf{A} + 1.459\,\mathbf{B} + 2.663\,\mathbf{V} \quad (8)$$

DISCUSSION

When data for the various end points shown in Table 1 are fitted to equation [1], equations are obtained with different intercepts (c) and different coefficients (e-l). How all the data can be expressed in one equation is shown in Fig. 2, that is based on the simple equation [9].

$$\boldsymbol{Y} = \mathrm{m}\mathbf{X} + \mathrm{c} \quad (9)$$

Two sets of data points are shown in Fig. 2, those for equation B having a different slope and very different intercept to those for equation A. An indicator variable adjusts the points for equation B so that both sets of points have the same intercept. Then it is possible to derive an equation for the combined set of points with an 'average' slope. The SD value for the combined equation will not be as good as the separate SD values, but provided that the separate equations have slopes that are not too far apart, the combined equation may be judged to be reasonable, and, of course, will cover a much larger range of values.

The coefficients of the indicator variables in equation [3] yield information as to the sensitivity of the various processes, for the specific cases where the same units are used, and where the form of the dependent variable is the same. From Table 2 it can be seen that a number of processes conform to this, and can then be ranked for sensitivity. The indicator variable for nasal pungency irritation is very nearly zero, and so, on the given experimental protocol, the sensitivity towards irritants is the same for eye irritation and nasal pungency. The mouse assay is a little more sensitive than sensory irritation, **Ird50** = 0.44 log units, and the olfactory system for odor detection thresholds is very much more sensitive than sensory irritation or the mouse assay, **Iodt** = 2.77 log units.

Our preferred equations for sensory irritation thresholds, equation [4] and equation [6], are statistically very good, they cover a very wide range of VCs, and have a predictive ability of about 0.36 log units in log (1/SIT). This is good enough for the prediction of SIT values for a host of atmospheric pollutants. Although equation [4] covers a very large range of VCs, great care must still be taken over compounds that might act through a specific mechanism, because there is no reason why compounds that act by a specific mechanism in one test to one species should act in the same way in another test to another species. Amines and isocyanates were classed as acting via a chemical mechanism in the mouse assay, (Alarie *et al*., 1995 and 1996; Nielsen *et al*., 2007) and they might act in a similar way in an eye irritation threshold test, but this does not necessarily follow from the mouse assay results. In addition, we have recently shown that on ascending a homologous series of VCs, for example n-alkyl acetates or n-alcohols, the sensory irritation, i.e., chemesthetic, activity of the VC does not continually increase, but a point is reached at which the activity begins to decrease (Cometto-Muñiz *et al*., 2005a, 2005b, 2006 and 2007, Cain et al., 2006) This 'cut-off' is possibly due to an effect of VC size (perhaps the length of a VC) that inhibits interaction with human chemesthetic receptors (Cometto-Muñiz et al., 2007, Cometto-Muñiz and Abraham, 2008). Hence care must be taken over the use of equation [4] for the prediction of sensory irritation thresholds of large VCs. Furthermore we note that the absolute value of sensory irritation thresholds specifically refer to a given experimental protocol (Cometto-Muñiz et al., 2000 and 2002).

Finally, we comment on the implications of the general equation [4] for the mechanism of non-lethal toxic and biological action of VCs. It has been suggested (Abraham *et al*., 1994) that the

activity of gaseous VCs takes place through a two-stage mechanism: (1) a VC is transferred from the gas phase to a receptor phase or area, and (2) the VC then interacts with a receptor. The observation that VC activities of non-reactive compounds in a wide variety of biological systems can be well correlated by the same equation indicates that the main step in the two-stage mechanism is transfer from the gas phase to receptor phases or areas. The receptors themselves discriminate only marginally between the different VCs. The coefficients e-l in equation [4] are certainly comparable with coefficients in equation [1] for transfer from the gas phase to phases such as wet pentanol (Abraham *et al.*, 2008b), wet butyl acetate (Sprunger *et al*., 2008), and, possibly quite significantly, the peptide model N-methylformamide (Abraham *et al.*, 2009). The coefficients are not far from transfers from the gas phase to the biological phases brain and muscle (although some way from fat), as shown in Table 3 (Abraham and Ibrahim, 2006; Abraham *et al*., 2006a and 2006b). Naturally, there will be differences in the final biological phase (the receptor phase or area) and so at a more detailed level than our general equation represents, various equations on the lines of equation [1] are necessary to correlate the different processes.

In the case of odor detection thresholds, the large number of outliers to equation [4] suggests that interaction with a receptor, stage two, now plays a significant part, and that the receptor (s) does discriminate between VCs (see, for example, Malnic, 2007).

The supplementary table contains a full list of all the compounds studied, the corresponding biological and toxicological data and the descriptors used in the regression equations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work described in this article was supported, in part, by research grants R01 DC 005003 and DC 002741 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, USA.

Abbreviations

VC	volatile compound
QSAR	quantitative structure-activity relationship
NPT	nasal pungency threshold
EIT	eye irritation thresholds
ODT	odor detection threshold
RD_{50}	upper respiratory tract irritation in mice
ppm	parts per million
atm	atmospheres

References

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.

Abraham MH. Scales of hydrogen bonding: Their construction and application to physicochemical and biochemical processes. Chem Soc Rev 1993;22:73–83.

Abraham MH, Nielsen GD, Alarie Y. The Ferguson principle and an analysis of the biological activity of gases. J Pharm Sci 1994;83:680–688. [PubMed: 8071821]

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 1998a;12:403–408.

Abraham MH, Kumarsingh R, Cometto-Muñiz JE, Cain WS. An algorithm for nasal pungency thresholds in man. Arch Toxicol 1998b;72:227–232. [PubMed: 9587018]

Abraham MH, Kumarsingh R, Cometto-Muñiz JE, Cain WS. A quantitative structure-activity relationship (QSAR) for a Draize eye irritation data base. Toxicol in Vitro 1998c;12:201–207. [PubMed: 20654402]

Abraham MH, Gola JMR, Cometto-Muñiz JE, Cain WS. A model for odor thresholds. Chem Senses 2002;27:95–104. [PubMed: 11839607]

Abraham MH, Ibrahim A, Zissimos AM. Determination of sets of solute descriptors from chromatographic measurements. J Chromatogr A 2004;1037:29–47. [PubMed: 15214659]

Abraham MH, Ibrahim A. Air to fat and blood to fat distribution of volatile organic compounds and drugs: linear free energy analyses. Eur J Med Chem 2006;41:1430–1438. [PubMed: 16996652]

Abraham MH, Ibrahim A, Acree WE Jr. Air to muscle and blood/plasma to muscle distribution of volatile organic compounds and drugs: linear free energy analysis. Chem Res Toxicol 2006a;19:801–808. [PubMed: 16780359]

Abraham MH, Ibrahim A, Acree WE Jr. Air to brain, blood to brain and plasma to brain distribution of volatile organic compounds: linear free energy analysis. Eur J Med Chem 2006b;41:494–502. [PubMed: 16516353]

Abraham MH, Sánchez-Moreno R, Cometto-Muñiz JE, Cain WS. A quantitative structure-activity analysis on the relative sensitivity of the olfactory and the nasal trigeminal chemosensory systems. Chem Senses 2007;32:711–719. [PubMed: 17573355]

Abraham MH, Acree WE Jr. 2007 unpublished work.

Abraham MH, Acree WE Jr, Mintz C, Payne S. Effect of anesthetic structure on inhalation anesthesia: implications for the mechanism. J Pharm Sci 2008a;97:2373–2384. [PubMed: 17847069]

Abraham MH, Nasezadeh A, Acree WE Jr. Correlation and prediction of partition coefficients from the gas phase and from water to alkan-1-ols. Ind Eng Chem Res 2008b;47:3990–3995.

Abraham MH, Acree Jr, Cometto-Muñiz JE. Partition of compounds from water and from air into amides. New J Chem 2009;33:2034–2043.

Abraham MH, Acree WE Jr. Prediction of convulsant activity of gases and vapors. Eur J Med Chem 2009;44:885–890. [PubMed: 18603335]

Alarie Y. Irritating properties of airborne materials to the upper respiratary tract. Arch Environ Health 1966;13:433–449. [PubMed: 5921282]

Alarie Y. Sensory irritation by airborne chemicals. CRC Crit Revs Toxicol 1973;2:299–363. [PubMed: 4131690]

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. [PubMed: 7676461]

Alarie Y, Schaper M, Nielsen GD, Abraham MH. Estimating the sensory irritating potency of airborne nonreactive volatile organic chemicals and their mixtures. SAR & QSAR in Environ Res 1996;5:151–165. [PubMed: 9114512]

Bagnall RD, Bell W, Pearson K. New inhalation anaesthetics: I. fluorinated 1,3-dioxolane derivatives. J Fluorine Chem 1977;9:359–375.

Bagnall RD, Bell W, Pearson K. New inhalation anaesthetics: II. fluorinated methyl propyl ethers. J Fluorine Chem 1978;11:93–107.

Bagnall RD, Bell W, Pearson K, Jeater A. New inhalation anaesthetics: III. fluorinated aliphatic ethers. J Fluorine Chem 1979a;13:23–140.

Bagnall RD, Bell W, Pearson K. New inhalation anaesthetics: IV. fluorinated propanes. J Fluorine Chem 1979b;13:209–223.

Bagnall RD, Bell W, Pearson K. New inhalation anaesthetics: V. fluorinated butanes (and butanes). J Fluorine Chem 1979c;13:325–335.

Bowen KC, Flanagan KB, Acree WE Jr, Abraham MH, Rafols C. Correlation of the toxicity of organic compounds to tadpoles using the Abraham Model. Science Total Environ 2006;371:99–109.

Cain WS, Lee NS, Wise PM, Schmidt R, Ahn BH, Cometto-Muñiz JE, Abraham MH. Chemesthesis from volatile organic compounds: Psychophysical and neural responses. Physiol Behav 2006;88:317–324. [PubMed: 16806320]

Cavanaugh JE. Unifying the derivations for the Akaike and corrected Akaike information criteria. Statistics and Probability Letters 1997;33:201–208.

Cometto-Muñiz, JE. Physicochemical basis for odor and irritation potency of VOCs. In: Spengler, JD., et al., editors. Indoor Air Quality Handbook. New York: McGraw-Hill; 2001. p. 20.1-20.21.

Cometto-Muñiz JE, Cain WS, Hiraishi T, Abraham MH, Gola JMR. Comparison of two stimulus-delivery systems for measurement of nasal pungency thresholds. Chem Senses 2000;25:285–291. [PubMed: 10866987]

Cometto-Muñiz JE, Cain WS, Abraham MH, Gola JMR. Psychometric functions for the olfactory and trigeminal detectability of butyl acetate and toluene. J Appl Toxicol 2002;22:25–30. [PubMed: 11807926]

Cometto-Muñiz JE, Cain WS, Abraham MH. Detection of single and mixed VOCs by smell and by sensory irritation. Indoor Air 2004;14 (Suppl 8):108–117. [PubMed: 15663466]

Cometto-Muñiz JE, Cain WS, Abraham MH. Molecular restrictions for human eye irritation by chemical vapors. Toxicol Applied Pharmacol 2005a;207:232–243.

Cometto-Muñiz JE, Cain WS, Abraham MH. Determinants for nasal trigeminal detection of volatile organic compounds. Chem Senses 2005b;30:627–642.

Cometto-Muñiz JE, Cain WS, Abraham MH, Sánchez-Moreno R. Chemical boundaries for detection of eye irritation in humans from homologous vapors. Toxicol Sci 2006;91:600–609. [PubMed: 16543295]

Cometto-Muñiz JE, Cain WS, Abraham MH, Sánchez-Moreno. Cutoff in detection of eye irritation from vapors of homologous carboxylic acids and aliphatic aldehydes. Neuroscience 2007;145:1130–1137. [PubMed: 17270354]

Cometto-Muñiz JE, Cain WS, Abraham MH, Sánchez-Moreno R. Concentration-detection functions for eye irritation evoked by homologous n-alcohols and acetates approaching a cut-off point. Exp Brain Res 2007;182:71–79. [PubMed: 17503026]

Cometto-Muñiz JE, Abraham MH. A cut-off in ocular chemesthesis from vapors of homologous alkylbenzenes and 2-ketones as revealed by concentration-detection functions. Toxicol Appl Pharmacol 2008;230:298–303. [PubMed: 18485434]

Davies RH, Bagnall RD, Jones WGM. A quantitative interpretation of phase effects in anaesthesia. Int J Quantum Chem: Quantum Biology Symp 1974;1:201–212.

Davies RH, Bagnall RD, Bell W, Jones WGM. The hydrogen bond proton donor properties of volatile halogenated hydrocarbons and ethers and their mode of action in anaesthesia. Int J Quantum Chem: Quantum Biology Symp 1976;3:171–185.

Dearden JC, Cronin M, Kaiser KLE. How not to develop a quantitative structure-activity or structure-property relationship (QSAR/QSPR). SAR & QSAR in Environ Res 2009;20:241–266. [PubMed: 19544191]

Eger EI II, Koblin DD, Sonner J, Gong D, Laster MJ, Ionescu P, Halsey MJ, Hudlicky T. Nonimmobilizers and transitional compounds may produce convulsions by two mechanisms. Anesth Analg 1999;88:884–892. [PubMed: 10195542]

Famini GR, Aguiar D, Payne MA, Rodriquez R, Wilson LY. Using the theoretical linear solvation energy relationship to correlate and predict nasal pungency thresholds. J Mol Graphics Model 2002;20:277–280.

Hau KM, Connell DW. Quantitative structure-activity relationships (QSARs) for odor detection thresholds of volatile organic compounds (VOCs). Indoor Air 1998;8:23–33.

Hau KM, Connell DW, Richardson BJ. Quantitative structure-activity relationship for nasal pungency thresholds of volatile organic compounds. Toxicol Sci 1999;47:91–98.

Hawkins DM. The problem of overfitting. J Chem Inf Comput Sci 2004;44:1–12. [PubMed: 14741005]

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 RD_{50}) of volatile organic chemicals. Chemosphere 2006;63:11142–1153.

Malnic B. Searching for the ligands of odorant receptors. Mol Neurobiol 2007;35:175–181. [PubMed: 17917106]

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 Toxicol 1984;22:661–664.

Nielsen GD, Wolkoff P, Alarie Y. Sensory irritation: risk assessment approaches. Reg Toxicol Pharmacol 2007;48:6–18.

Roberts DW. QSAR for upper-respiratory tract irritation. Chem-Biol Interactions 1986;57:325–345.

Schulz TW, Yarbrough JW, Hunter RS, Aptula AO. Verification of structural alerts for Michael acceptors. Chem Res Toxicol 2007;20:1359–1363. [PubMed: 17672510]

Sewell JC, Sear JW. Derivation of preliminary three-dimensional pharmacophores for nonhalogenated volatile anesthetics. Anesth Analg 2004;99:744–751. [PubMed: 15333405]

Sewell JC, Sear JW. Determinants of volatile general anesthetic potency. A preliminary three-dimensional pharmacophore for halogenated anesthetics. Anesth Analg 2006;102:764–771. [PubMed: 16492826]

Sprunger LM, Proctor A, Acree WE Jr, Abraham MH, Benjelloun-Dakhama N. Correlation and prediction of partition coefficient between the gas phase and water, and the solvents dry methyl acetate, dry and wet ethyl acetate, and dry and wet butyl acetate. Fluid Phase Equilibr 2008;270:30–44.

Takahashi Y, Koike M, Honda H, Ito Y, Sakaguchi H, Suzuki H, Nishiyama N. Development of the short time exposure (STE) test: an *in vitro* eye irritation test using SIRC cells. Toxicol in Vitro 22:760–770. [PubMed: 18248950]

Yarbrough JW, Schultz TW. Abiotic sulfhydryl reactivity: a predictor of aquatic toxicity for carbonyl-containing α,β-unsaturated compounds. Chem Res Toxicol 2007;20:558–562. [PubMed: 17319700]

Won A, Oh I, Laster MJ, Popovich J, Eger EI II, Sonner JM. Chirality in anesthesia I: minimum alveolar concentration of secondary alcohol enantiomers. Anesth Analg 2006;103:81–84. [PubMed: 16790631]

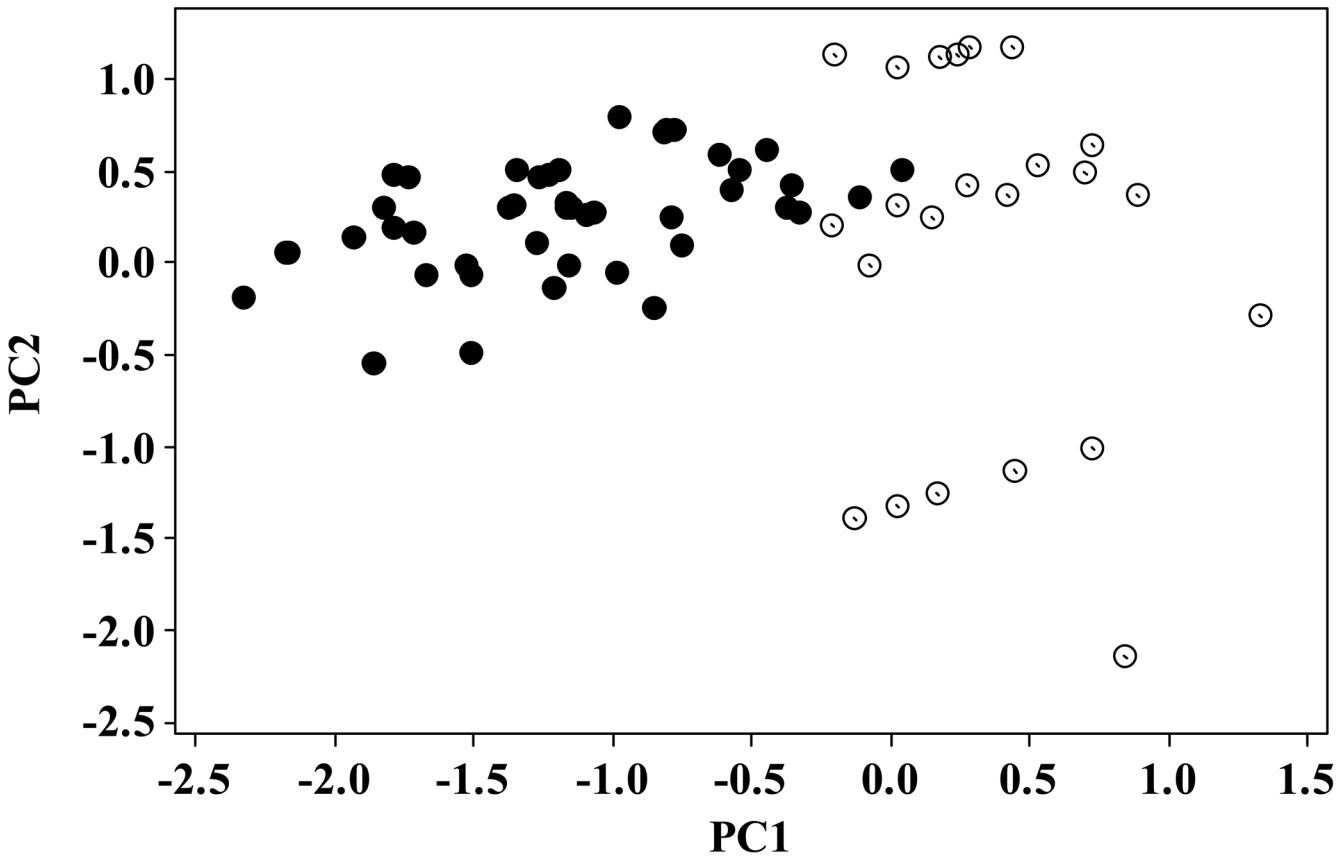

Fig. 1.
Plot of PC2 against PC1 for eye irritation ○ and inhalation anesthesia (Davies) •.

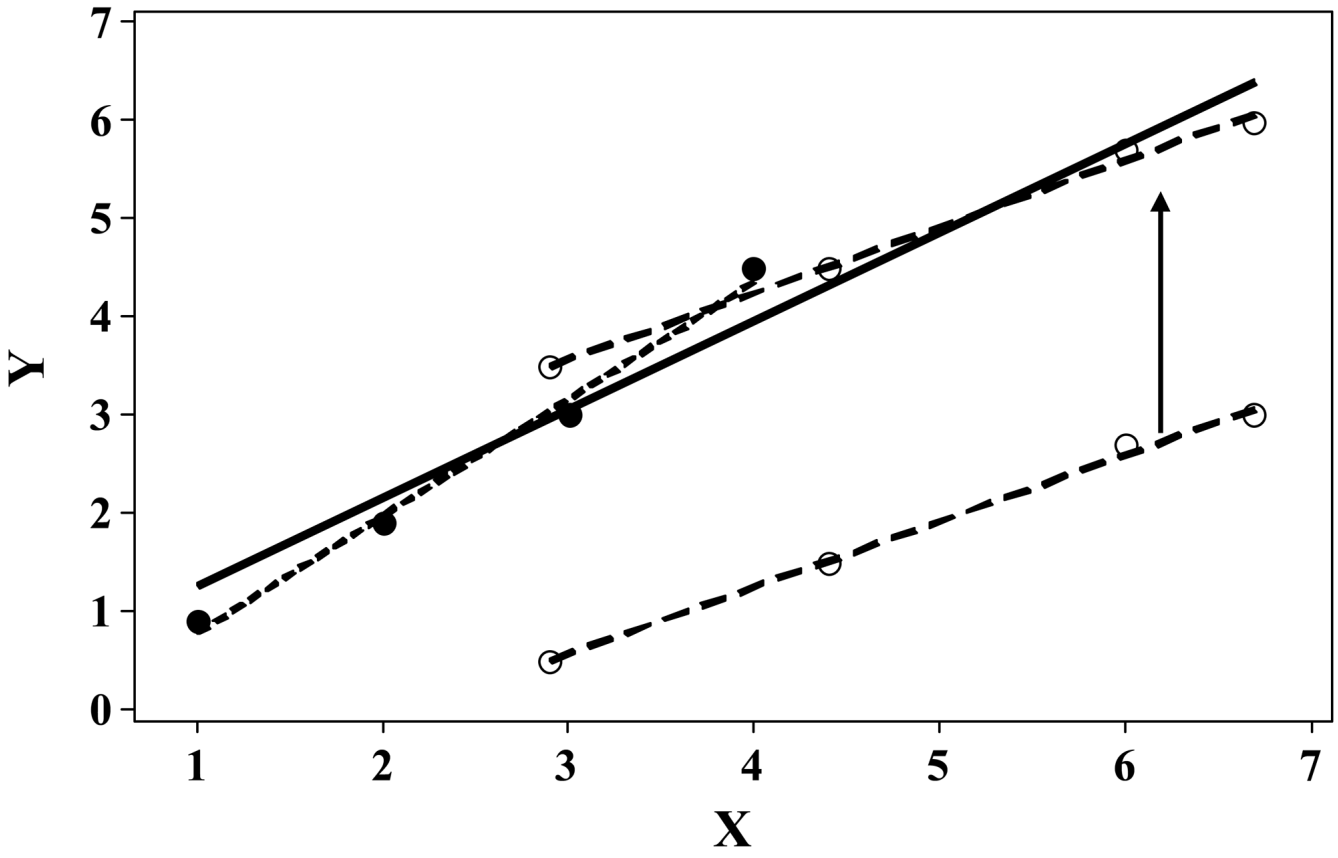

Fig. 2.
Plots of equations of the form Y = mX + c; • equation A; ○ equation B; vertical arrow → shows the effect of an indicator variable. Dashed lines are for the separate equations, full line for the combined equation.

Table 1

The number of VCs in the various processes that have been used

Process	Units	Y	Indicator	Number of VCs	
				Total	Outliers
Eye irritation thresholds	ppm	log(1/EIT)	None	23	0
EIT from Draize scores	ppm	log(D/P°) [a]	Idr	72	0
Odor detection thresholds	ppm	log(1/ODT)	Iodt	64	20
Nasal pungency thresholds	ppm	log(1/NPT)	Inpt	48	0
Inhalation anesthesia in rats	atm	log(1/MAC)	Imac	147	0
Upper respiratory irritation in mice	ppm	log(1/RD_{50})	Ird50	147	53
Gaseous anesthesia in tadpoles	mol/L	log(1/C)	Itad	130	4
Convulsant activity of vapors in rats	atm	log(1/CON)	Icon	44	0
Inhalation anesthesia in mice	vol %	log(1/vol)	Idav	45	0
Total				720	77

[a] D is the Draize eye score and P^{o} is the VC saturated vapor pressure.

Table 2

Determination of the efficiency of equations

Equation	**P**	**SD**	**r^2**	**F**	**AIC**
Equation [3]	13	0.357	0.992	6083	513.4
Remove **Inpt**	12	0.357	0.992	6599	511.6
Remove **Inpt, E,** Equation [4]	11	0.357	0.992	7199	510.5
Remove **Inpt, E, Ird50**	10	0.375	0.991	7159	573.9

Table 3

Coefficients in equation [1] for a number of systems

System	c	e	s	a	b	l
Equation [3]	−7.80	0.03	1.58	3.42	1.37	0.757
Gas to wet pentanol	−0.11	0.00	1.19	3.61	1.67	0.721
Gas to wet butyl acetate	−0.66	0.06	1.67	3.37	0.82	0.832
Gas to N-methylformamide	−0.25	−0.14	1.66	4.15	0.82	0.739
Gas to brain	−0.99	0.26	0.41	3.36	2.02	0.591
Gas to muscle	−1.04	0.21	0.72	3.24	2.47	0.463
Gas to fat	−0.05	0.05	0.73	1.78	0.33	0.743