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An assessment of air quality reflecting the chemosensory irritation impact of mixtures of volatile organic compounds. Michael H. Abraham, ^{*a} Joelle M. R. Gola,^a and J. Enrique Cometto-Muñiz^b

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ABSTRACT

We present a method to assess the air quality of an environment based on the chemosensory irritation impact of mixtures of volatile organic compounds (VOCs) present in such environment. We begin by approximating the sigmoid function that characterizes psychometric plots of probability of irritation detection (Q) versus VOC vapor concentration to a linear function. First, we apply an established equation that correlates and predicts human sensory irritation thresholds (SIT) (i.e., nasal and eye irritation) based on the transfer of the VOC from the gas phase to biophases, e.g., nasal mucus and tear film. Second, we expand the equation to include other biological data (e.g., odor detection thresholds) and to include further VOCs that act mainly by "specific" effects rather than by transfer (i.e., "physical") effects as defined in the article. Then we show that, for 72 VOCs in common, Q values based on our calculated SITs are consistent with the Threshold Limit Values (TLVs) listed for those same VOCs on the basis of sensory irritation by the American Conference of Governmental Industrial Hygienists (ACGIH). Third, we set two equations to calculate the probability (Qmix) that a given air sample containing a number of VOCs

could elicit chemosensory irritation: one equation based on response addition (Qmix scale: 0.00 to 1.00) and the other based on dose addition (1000*Qmix scale: 0 to 2000). We further validate the applicability of our air quality assessment method by showing that both Qmix scales provide values consistent with the expected sensory irritation burden from VOC mixtures present in a wide variety of indoor and outdoor environments as reported on field studies in the literature. These scales take into account both the concentration of VOCs at a particular site and the propensity of the VOCs to evoke sensory irritation.

1. Introduction

A number of methods have been used to quantify the toxicological effects of volatile organic compounds, VOCs. The best known method is probably the 'mouse assay' of Alarie, that uses upper respiratory tract irritation in mice to define an RD₅₀ value, the vapour concentration of a VOC in ppm that leads to a 50% reduction in the rate of breathing of a mouse (Alarie, 1966, 1973). In turn, the threshold limit values, TLVs, established by ACGIH (ACGIH, 2008) are based on a review of existing published and peer-review literature in various scientific disciplines (e.g., industrial hygiene, toxicology, occupational medicine, and epidemiology). Recommendations for the establishment of LOAEL (lowest observed adverse effect level on humans) from RD₅₀ values have been set out (Kuwabara et al., 2007), as well as NOAEL (noobserved-adverse effect level on humans), again from RD₅₀ values (Nielsen et al., 2007). Other quantitative assessments include odor detection thresholds in humans, ODTs, (Devos et al., 1990; US EPA, 1992; van Gemert, 2003; Nagata, 2003; Cometto-Muñiz, 2001b) as well as nasal pungency thresholds, NPTs, and eye irritation thresholds, EITs, in humans (Cometto-Muñiz, 2001b). It has recently been proposed (Jakubowski and Czerczak, 2010) that an equation for the prediction of NPTs (Abraham et al., 2001) could be used to predict occupational exposure limits of VOCs.

The above methods of quantification of the toxicological effects of VOCs refer to the effects of individual VOCs. Several studies of sensory irritation thresholds (NPTs and EITs) from mixtures of VOCs have shown various levels of additivity that, to a first approximation, are not-too-far from complete additivity (Nielsen et al., 1988; Cometto-Muñiz et al., 1997; 1999; 2001a; 2004a; 2004b). So are results from studies on ODTs (Cometto-Muñiz et al., 2003; 2005b; Wise et al., 2007; Miyazawa et al., 2009). To extend occupational exposure limits to mixtures of VOCs, additivity of effects has been suggested (Alarie et al., 1996). However, there appears to be no application of the additivity of sensory irritation effects to any assessment of the overall air quality due to mixtures of VOCs. It is the aim of this paper to set out such an assessment.

2. Methods

2.1 The Psychometric plots

We start with the psychometric plots obtained from the probability of sensory irritation detection, Q, of a given VOC as a function of its gaseous concentration, log P with P in ppm (Cometto-Muñiz et al., 1999; 2001a; 2002; 2004a; 2004b; 2007b; 2008; Cain et al., 2006). As for the determination of thresholds, this involves a panel of human subjects. The outcome, for a given VOC, is a probability-concentration plot known as a psychometric plot. The general shape of such a plot is shown in Fig. 1, where Q is the probability of detection corrected for chance (Macmillan and Creelman, 1991). For sensory irritation, the plot is extraordinarily steep, and the difference in log P corresponding to chance detection, Q = 0, and perfect detection, Q = 1, is typically around one log unit, e.g. (Cometto-Muñiz et al., 2002; 2004b). This is indicated on the plot by Δ , where $2\Delta =$ one log unit in log P. The log P value corresponding to Q = 0.5, is that of the detection threshold, shown as log P_{0.5}.

These psychometric plots are very important indeed. The probability of detecting a VOC tails off to zero within a relatively narrow concentration range as log P becomes progressively smaller. Below a gaseous concentration of $(\log P_{0.5} - \Delta)$, the probability of detecting a VOC is zero. Since $\Delta = 0.5$ log units only, the probability decreases to zero quite sharply.



Fig. 1. Typical shape of a psychometric plot of detection probability of a VOC by sensory irritation against its vapor concentration.

A second very important finding is that of a cut-off effect. On ascending a homologous series of VOCs, the potency of a VOC increases as shown in Table 1.

Table 1

Some EIT values (from Abraham et al., 2003)

VOC	Log(1/EIT)
Ethanol	-4.76
Propan-1-ol	-3.74
Butan-1-ol	-3.37
Hexan-1-ol	-2.60

What is evident (Cometto-Muñiz et al., 1998b; 2005a; 2005c; 2006; 2007a; 2007b; 2008b; Cometto-Muñiz et al., 2010; Cain et al., 2006) is that this increase in sensory irritation potency does not simply carry on along a homologous series, but a homolog is reached where the potency declines to zero. For each of the alcohols in Table 1, as the gaseous concentration of alcohol is increased, Q in the psychometric plots approaches unity. But Q for decan-1-ol never reaches beyond 0.5 no matter what is the gaseous concentration, and the same happens for undecan-1-ol (Cometto-Muñiz et al., 2005a; 2007b). For still higher homologues the maximum value of Q will be

around zero. For the carboxylic acids, Q for hexanoic acid reaches values greater than zero, but Q for heptanoic and octanoic acids are definitely near zero (Cometto-Muñiz et al., 2005c; 2007a). This cut-off effect has been found in all the homologous series studied (Cometto-Muñiz, 2001b; Cometto-Muñiz et al., 2010). It looks like the sensory irritation receptive system is very broad in that it will accept almost any VOC, unless the VOC exceeds a critical size that allows it to interact effectively with the relevant receptors. One measure of 'size' is the VOC descriptor, *L* (the gas-hexadecane partition coefficient at 25° C, see later), and it is useful to compare the *L*-values at the cut-off points for various series, see Table 2 (Cometto-Muñiz et al. 2005a; 2007a; 2007b). It seems that any VOC with an *L*-value more than about 6.1 will not be effective in eliciting sensory irritation.

Table 2

Values of L at various cut-off points along homologous series.

VOC	L
Undecan-1-ol	6.13
Decyl acetate	6.24
Heptanoic acid	4.18
Heptyl benzene	6.22
Tridecanone	6.67
Dodecanal	6.31

The psychometric plots can be fitted to sigmoid type functions, but this is not very helpful, because the constants for the function vary from VOC to VOC and in any case are known only for a limited number of VOCs. Advantage can be taken of the fact that Δ in Fig. 1 does not vary very much with the VOC – what varies appreciably is the position of the curve along the log P axis. This is defined by the detection threshold for the VOC, which corresponds to the point shown as Q = 0.5 and log P = log P_{0.5}.

An approximation to the psychometric curve is shown in Fig. 2. The full line is given by Eq. (1), where SIT is the sensory irritation threshold.

 $Q = 0.5 + [\log P/ppm - \log SIT]$ (1)

A point to consider is that Eq. (1) will yield negative values of Q when the gaseous concentration is less than (log P_{0.5} - Δ), i.e. less than (log SIT - 0.5). However this can easily be overcome by setting Q = 0 for log P < (log SIT - 0.5). In addition, one can set Q = 1 for log P > (log SIT + 0.5), leading to the approximation shown in Fig. 2.



Fig. 2. The approximation to the sensory irritation psychometric plot.

In order to apply Eq. (1), it is necessary to calculate (predict) the sensory irritation threshold, SIT, for any VOC, as described in the next section.

2.2 Sensory irritation thresholds, SIT.

The general equation, Eq. (2) is a well-known equation for the correlation and prediction of a large number of physicochemical and biological/toxicological processes. Eq. (2) is mostly used for processes that involve the transfer of a VOC from the gas phase to some condensed phase (Abraham, 1993; Abraham et al. 2004). The condensed phase may be a standard organic solvent, or may be a biophase such as blood, brain, muscle, nasal mucus, tear film, etc.

$$Y = c + eE + sS + aA + bB + lL$$
⁽²⁾

In Eq. (2) the dependent variable, Y, is some physicochemical or biological property of a series of VOCs in a given system. For example, Y can be log (1/NPT) where NPT is the nasal pungency threshold in humans for a series of VOCs (Abraham et al., 2010a) or *Y* can be the more general sensory irritation threshold log (1/SIT). We use 1/NPT or 1/SIT so that the larger the value of log (1/SIT) the more potent, or active, is the VOC. The independent variables in Eq. (2) are VOC descriptors as follows (Abraham, 1993; Abraham et al. 2004): *E* is the VOC excess molar refractivity in units of (cm³ mol⁻¹)/10, *S* is the VOC dipolarity/ polarizability, and *A* and *B* are the overall or summation hydrogen bond acidity and basicity of the VOC. *L* is the logarithm of the VOC gas-hexadecane partition coefficient at 25°C, and functions as a descriptor of the size of the VOC. The coefficients in Eq. (2) are evaluated through multiple linear regression analysis.

The descriptors of the VOCs are obtained from various physicochemical properties, including gas chromatography, gas to solvent and water to solvent partitions, as set out before (Abraham, 1993; Abraham et al. 2004). In addition, commercial software is available for the calculation of the VOC descriptors just from structure (Absolv, 2014). Although Eq. (2) has been applied to eye irritation thresholds and nasal pungency thresholds (Abraham et al., 2001), the number of VOCs in each study has not been very large. More recently (Abraham et al., 2010b), Eq. (2) has been applied to the biological activity of VOCs in general, including eye irritation thresholds and nasal pungency thresholds. The resulting equation puts all such activity on the same scale as SITs, but now includes a great deal more data. Note that Eq. (3) refers to VOCs that act through physical effects.

$$Log (1/SIT) = Y = -7.805 + 1.558 S + 3.342 A + 1.421 B + 0.771L + \sum f.F$$
(3)

$$N = 631, SD = 0.348, R^2 = 0.992, FS = 6242.7$$

In Eq. (3), the term $\sum f F$ includes a set of indicator variables, F, to put other biological data (e.g., odor detection thresholds, ODTs) on the same scale as SIT values; the coefficients corresponding to the indicator variables are denoted as f. Details of the $\sum f F$ term are discussed under Eq. (5), and a full account of the method of indicator variables has been given (Abraham et al., 2012). N is the number of data points; this is not the same as the number of VOCs, because many VOCs are in more than one data set. The actual number of different VOCs is 420. SD is the regression standard deviation, R is the correlation coefficient and FS is the F-statistic. Included in Eq. (3) are not only the rapid (seconds) eye irritation and nasal pungency thresholds in

humans, but the longer term (minutes) mouse assay (Alarie 1966; Alarie 1973; Nielsen et al. 2007; Alarie et al, 1995, 1996, 1998a, 1998b) and very long term (minutes/hours) anesthetic effects (Abraham et al. 2008). VOCs have been divided into those that act by a 'physical' and those that act by a 'chemical' mechanism (Abraham et al., 2010a; Alarie et al. 1995, 1996, 1998) noting that in the mouse assay test, it was possible to account for the RD₅₀ end point only for VOCs that acted by a 'physical' mechanism. A rather different terminology has been used in classifying the effect of VOCs on odor detection thresholds, ODTs (Abraham et al. 2007). VOCs were divided into those that acted by 'physical' effects (e.g., transfer driven effects in which small structural changes in VOC evoke predictable, and rather small, changes in biological activity) and 'specific' effects (e.g., those in which small structural changes in the VOC may evoke less predictable, and often large, changes in biological activity). Simple equations such as Eq. (2) apply only to VOCs that act through 'physical'. If it is necessary to include VOCs that act through 'specific' effects, then some extra descriptors that take these specific effects into account must be incorporated into the equation.

Furthermore, equations such as Eq. (3) will yield predicted values of SIT on a relative scale and not on any absolute scale. The constant term in Eq. (3) defines the relative scale, and in practical situations the constant term may not be the same as the term in Eq. (3), viz. -7.805, that is derived from experiments under laboratory conditions. Finally, VOCs with L > 6.1 are expected to have no sensory irritation effect because they are too large to interact and activate the receptive system.

2.3 Equations for the prediction of sensory irritation thresholds.

The most comprehensive equation constructed to date for SITs is Eq. (3), that includes 420 different VOCs. These VOCs all act through 'physical' effects. By and large the biological activity of the VOCs that act through physical effects is considerably smaller than the activity of VOCs that act through specific effects. It is therefore of very considerable importance to include VOCs that act through specific effects in any equation that is supposed to deal with VOCs in general.

One approach is to start with an equation for VOCs that act through physical effects, such as Eq. (3) and then to incorporate descriptors for various classes of

VOCs that act through specific effects. In this way, an equation for 353 odor detection thresholds (ODTs) was constructed (Abraham et al. 2012):

$$Log (1/ODT) = -1.560 + 0.398 E + 0.571 S + 1.103 A + 1.355 B + 0.580 L + \sum f.F$$
$$+ \sum g.G$$
(4)

 $N = 353, R^2 = 0.759, SD = 0.818, F = 70.7$

As in Eq. (3), the term $\sum f.F$ is a set of coefficients and indicator variables to put various collections of ODT values onto the same scale. Details of the $\sum f.F$ term and the $\sum g.G$ term are discussed under Eq. (5). The term $\sum g.G$ contains another set of coefficients and indicator variables for the various types of VOC that act through specific effects. Details are in Table 3. For example mercaptans with g = 3.817 are nearly 10,000 times as potent as expected from their physicochemical properties (*E*, *S*, *A*, *B*, *L*). Although the resulting equation, Eq. (4), contains a large number of terms, the equation is linear and is very easily computed.

Table 3

Coefficients of indicator variables in Eq. (4)

for VOCs that act through specific effects

VOCs	g
Mercaptans	3.817
Aldehydes	1.935
Carboxylic acids	1.462
Unsaturated esters	1.310

We used Eq. (3) as a starting point. Eq. (3) already includes ODT values for VOCs that act through physical effects, and so we then added VOCs that act specifically and for which ODT values were available (Devos et al., 1990; Nagata, 2003; Cometto-Muñiz and Cain, 1990, 1991, 1993, 1994; Cometto-Muñiz et al.,

1998a, 1998b; Cometto-Muñiz and Abraham, 2008a, 2008c, 2009a, 2009b, 2010a, 2010b; Hellman and Small, 1974; Rodriguez et al., 2011; Czerny et al., 2011). We also included VOCs that act specifically, and had been studied in the mouse assay (Alarie et al., 1995, 1996, 1998; Schaper 1993). Other sets of data we used include those for inhalation anesthesia (Abraham et al., 2008), gaseous convulsant activity (Abraham and Acree, 2009), the Draize rabbit eye test (Abraham et al., 2003) and tadpole narcosis corrected to the gaseous state (Bowen et al., 2006). The final equation is Eq. (5). The list of coefficients for the different scales, *f*, and for the VOCs that act specifically, *g*, is given in Table 4. In the data base that we constructed, there were a number of VOCs with two specific sites in the molecule. We found that it was necessary to include only the most specific site, that is the site with the largest *g*-coefficient. For compounds with two identical specific sites, such as the α, ϕ -diaminoalkanes, we took G = 1 (i.e., one site) just as for the monoaminoalkanes.

Eq. (5) now contains no less than 1641 data points, and covers quite a range of VOCs that act specifically. We include the additional leave-one-out statistics *PRESS* and Q^2 , and give also the predicted standard deviation, *PSD*. The latter is no more than 0.65 log units, small enough to use Eq. (5) to predict further values of log (1/SIT) for VOCs that act through physical effects (non-reactive) and for the particular types of VOC in Table 4 that act specifically (reactive).

Log (1/SIT) =
$$Y = -7.282 + 0.074 E + 1.328 S + 2.851 A + 1.191 B + 0.684 L + $\sum f.F$
+ $\sum g.G$ (5)
 $N = 1641, SD = 0.633, R^2 = 0.962, F = 1163.3$
 $PRESS = 688.02, Q^2 = 0.959, PSD = 0.655$$$

The method of indicator variables used to obtain equation (5) has been set out in detail (Abraham et al. 2012). The NPT system is defined as the standard system and for all compounds F(NPT) = 0. For other systems such as the mouse test system, all compounds with mouse values take F(mouse) = 1 and compounds with no mouse values have F(mouse) = 0. Similarly for all other systems. The $\sum f.F$ term is very important because it allows a variety of effects to be analyzed in one single equation. The method has been discussed before (Abraham et al. 2012). Values of *f* are listed in

Table 4. By definition *f* for the NPT scale is zero. Interestingly, *f* for eye irritation thresholds is also zero, so that the EIT and NPT scales are the same. This is definitely not so for odor thresholds where there are differences of up to five log units between the scales. In order to apply Eq. (5) to the prediction of further values of log (1/SIT) it is not necessary to include any of the terms in *f*.*F*. These are used only if the biological data need to be calculated on some other scale. Thus if a calculation of SIT is made with f = 0.00 it will refer to the NPT scale (and to the EIT scale as well since both scales are the same). If SIT is calculated with f = 5.117 it will refer to ODT values, specifically on the Nagata scale. Odor pollution is often regarded as a specific air quality issue on its own, so that there may be some merit in establishing a separate assessment regarding odor pollution on similar lines to the present method for air quality regarding sensory irritation. We intend to pursue this in the future.

The $\sum g.G$ term is obtained in essentially the same way. For compounds that act through physical effects G = 0. Mercaptans act through specific effects and so for mercaptans that have SIT values G(mercaptan) = 1 and for mercaptans with no SIT values G(mercaptan) = 0. For disulfides that have SIT values G(disulfide) = 1 and for disulfides that have no SIT values G(disulfide) = 0. Then values of SIT are correlated against the usual descriptors plus the F-indicator variables and plus the G-indicator variables. The various g-values show how various classes of compound behave by comparison to compounds that act through physical effects. Mercaptans are more potent by 4.146 log units, allyl compounds are more potent by 1.733 log units. As shown before (Abraham et al. 2012) the method of indicator variables will only apply if the difference between the observed SIT values for compounds in two particular series is constant (within some experimental error).

Two factors that must be taken into consideration in the calculation/prediction of SIT values through Eq. (5). First, the constant term in Eq. (5) might not be the same in any practical situation. Second, VOCs with L > 6.1 will have no sensory irritation effect because they are too large to interact and activate the receptor(s). Once these factors have been taken into account, Q can be calculated for any given VOC through Eq. (1). It is important to note that the calculation of SIT values through Eq. (5) leaving out all the *f.F* terms yields SIT and, hence Q, on the NPT and EIT scale. If SIT values on any other scale are calculated through Eq. (5), one particular f-value is used. If the f-value is taken as f = 5.117 then the SIT refers to ODT values on the Nagata scale and the g-values then work to give SIT values on the ODT/Nagata scale for compounds that act through specific effects.

Table 4

Coefficients of indicator variables in Eq. (5) for VOCs that act through specific effects, g, and for VOCs on different scales, f

Compound type	g
RSH	4.146
RSR	2.233
RSSR	0.824
RSSSR	1.733
Aliphatic aldehydes	1.420
Aromatic aldehydes	-0.558
Carboxylic acids	-0.291
Aliphatic isocyanates	3.455
Aromatic isocyanates	1.700
Aliphatic amides	-2.160
Aliphatic amines	0.860
Anilines	-0.760
Unsaturated esters	1.085
Phenols	0.144
Aliphatic diols	1.401
Allyl compounds	1.733
Aliphatic diones	1.659
Data set	f
NPT, Abraham et al., $2007; f = 0.000$ by definition	0.000
EIT, Abraham et al., 2001, 2003.	0.000
ODT, Cometto-Muñiz and Cain ^a	2.738
ODT, Nagata, 2003	5.117
ODT, Hellman and Small, 1974	3.959
ODT, Cometto-Muñiz and Abraham ^b	5.062

ODT, Rodriguez et al., 2011	5.021
ODT, Czerny et al., 2011	1.802
ODT, Devos et al., 1990	3.868
Mouse test, Alarie et al., 1995, 1996, 1998; Schaper, 1993	0.469
Inhalation anesthesia, Abraham et al., 2008	6.730
Tadpole narcosis, Bowen et al., 2006	8.616
Inhalation convulsions, Abraham and Acree, 2009	7.040
Draize eye test, Abraham et al., 2003	0.526
Inhalation anesthesia, Davies et al., 1974, 1976	4.746

^a Cometto-Muñiz and Cain, 1990, 1991, 1993, 1994; Cometto-Muñiz et al., 1998a, 1998b. ^b Cometto-Muñiz and Abraham, 2008a, 2008c, 2009a, 2009b, 2010a, 2010b

The probability that a given air sample containing a number of VOCs could elicit sensory irritation, denoted as Qmix, can then be calculated from the response addition expression, Eq. (6), where the letters a, b. c. ... represent different VOCs.

$$Qmix = [1-(1-Qa)(1-Qb)(1-Qc)...]$$
(6)

The corresponding expression for dose addition is Eq. (7), (ACGIH, 2008).

$$Qmix = Ca/SITa + Cb/SITb \dots$$
(7)

In order that Q = 0.5 when C/SIT =1, Eq. (7) is amended to Eq. (8). This is required to make the equation compatible with the psychometric plots where Q is 0.5 at log P_{0.5} (that is when the vapor concentration (or pressure), C, is numerically the same as the sensory irritation threshold).

$$Qmix = 0.5*[Ca/SITa + Cb/SITb ..]$$
(8)

Note that Qmix obtained in this way cannot be negative, but can be greater than unity.

2.4 Comparison with data from ACGHI

As a preliminary assessment, we started with compiled threshold limit value (TLV) data for individual VOCs for which the TLV was set on the basis of sensory irritation (ACGIH, 2008) and calculated Q from the response addition equation, Eq. (6) and the dose addition equation, Eq. (8). The latter is the more useful in this context, and we found that with the constant term in Eq. (5) = -7.282 the calculated Q was very much less than Q = 1.00, the reference value that we associate with a TLV. For 72 VOCs from the ACGIH list we found that a constant term of -5.4 in the calculation of log SIT yielded values of Q consistent with the TLV values. It was not unexpected to find a constant term more positive than -7.282. The value of -7.282 is based on our NPT threshold values (Q = 0.5), and the -5.4 value is based on the ACGIH recommended maximum concentration at the workplace (referenced to Q = 1.0). The actual value of the constant term that is compatible with the ACGIH values of TLV based on sensory irritation may have considerable use in deriving further values of TLVs based on sensory irritation and not currently available.

3. Results and Discussion

One of the few suggestions for combining the effects of VOCs is that of Total Volatile Organic Compounds, TVOC, in which the concentrations of VOCs are simply summed. The limitations of the concept of TVOC has been well discussed (Molhave and Nielsen, 1992). Various pollution indices have been proposed, the most satisfactory being an indoor air pollution index, IAPI, (Sofuoglu and Moschandreas, 2003) but this includes the effect of bacteria and particulates as well as VOCs in terms of TVOC.

Various measured VOC concentrations over a wide range of environments have been reported. Unfortunately many reports have dealt with only a restricted number of VOCs and the results cannot be used as part of any comprehensive scheme. For example, in the European Union survey of schools (SINPHONIE, 2014) 456 sites covering 114 schools were surveyed, but analyses were carried out for only eight VOCs. Fortunately, several sources report data on a substantial number of VOCs. VOC concentrations in various outlets in an American shopping mall have been determined (Eklund et al. 2008), and data have been gathered on VOC concentrations in a wide variety of locations indoors (e.g., home, schools and commercial buildings) and outdoors (e.g., non-industrial and industrial areas) (Cometto-Muñiz and Abraham, 2015). Concentrations of VOCs in cars, buses and taxis in different towns in the world have also been reported (Geiss et al. 2009).

The required descriptors for VOCs in Eq. (5) are available (Abraham et al., 2010b, 2012; Absolv, 2014), and the indicator variables that act through specific effects, g in Eq. (5), can easily be determined from the VOC chemical structure. Then application of Eq. (5), with a constant of -5.4 will yield values of log (1/SIT) for each of the VOCs in a given mixture. Then application of Eq. (6) will lead to the response addition Qmix for the entire mixture, and application of Eq. (8) will yield the corresponding Qmix for dose addition. It is essential to note that these values of Qmix take into account not only the VOC air concentration but also the actual sensory irritation thresholds, SIT, of each VOC.

The data that we have used is summarized in Table 5, which gives the various locations, the number of VOCs analyzed, and references to the source of the data. For all these locations, dose addition Qmix and response addition Qmix were calculated using Eq. (6) and Eq. (8). Dose addition and response addition Qmix values range from 0 to almost 2 for the former and between 0 and 1 for the latter. Very small Qmix values were indeed calculated for locations such as homes and class rooms with no suspected issues. Large Qmix values were found for VOC concentrations above pig farms, which was highly expected.

The values of dose addition Qmix found for numerous locations were very small, effectively zero on a scale 0-1, so in order to put them on a more convenient scale, we multiplied the values of dose addition Qmix by 1000. These values thus scaled from 0-2000 are in Table 5. They provide a convenient scale for the comparison of air quality due to VOC mixtures in terms of chemosensory irritation. As regards the use of our method as an environmental warning index, we suggest that if the response addition Qmix value is larger than about 0.10, there is cause for concern. As we mentioned in "2.1 The Psychometric plots", the probability (Q) of detecting sensory irritation (i.e., nasal pungency or eye irritation) from a single VOC increases form Q = 0 to Q = 1 within about one order of magnitude of increase in concentration. Considering that, at least in environments such as homes and residential areas, any detectable level of true chemosensory mucosal irritation (not just odor) can be considered undesirable, a stringent limit, e.g., $Q \leq 0.10$ in the 0-1 Q-scale could be appropriate. This corresponds to a value of about 100 for 1000*Qmix dose addition in the 0-2000 scale. Nevertheless, in occupational environments, a less stringent

criterion could be chosen, depending, among other factors, on the time course of mucosal irritation (e.g., sensitization, adaptation) in the exposed population.

An important parameter for sensory irritation is the effect of exposure time. The few available data (see Shusterman et al., 2006; Wise et al., 2009) suggests that irritation will increase over many minutes, perhaps 30 minutes or more, before reaching a peak and fading. The ACGIH TLV values are concentrations that "represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects" (ACGIH, 2008). In turn, our measured and calculated (Eq. (3)) SITs refer to concentrations producing acute detection of sensory irritation by humans upon a time scale of just a few seconds (e.g., 1-5 sec), such that when Q = 1 nearly all subjects will experience immediate sensory irritation at that concentration. For the purpose of assessing air quality from mixtures of VOCs, we could ask if our method (Qmix) yields an instantaneous (i.e., acute) alert or an alert for a longer time scale such as the one intended for TLVs. Eq. (3) used with the original constant -7.282 reflects experimentally measured (NPTs and EITs) acute irritation responses (seconds), i.e., a very short-term exposure; but through the use of the alternative constant -5.4, we have found that the calculated log SIT values are consistent with the irritation-based TLVs for 72 VOCs, suggesting that the use of the latter constant (-5.4) in Eq. (3) produces an alternative outcome now relevant to long term exposures. Thus, both outcomes provide complementary information and can be employed to calculate and predict air quality from VOC mixtures (Qmix).

Table 5

Qmix Response Addition and Qmix Dose Addition for a number of locations.

Location	Qmix Response Addition	1000* Qmix Dose Addition	Number of VOCs	References
Inside pig farm	0.96	1940.03	30	Chmielowiec-Korzeniowska, 2009.
Commercial broiler house side wall	0.02	393.51	51	Trabue et al., 2010.

location, Southeastern US.				
Outside pig farm.	0.07	339.25	30	Chmielowiec-Korzeniowska, 2009.
Smoking areas in 10 Finnish restaurants.	0.27	297.24	16	Vainiotalo et al., 2008.
New home (Average)	0.08	289.31	53	Park et al., 2006. Logue et al., 2011. Takigawa et al., 2006.
Landfill dumping area in Hangzhou, China.	0.12	224.33	67	Ying et al., 2012.
Landfill leachate treatment plant in Hangzhou, China.	0.09	208.40	67	Ying et al., 2012.
Commercial broiler house production cycle building, Southeastern US.	0.00	167.21	54	Trabue et al., 2010.
Commercial broiler house empty building, Southeastern US.	0.00	134.27	40	Trabue et al., 2010.
Landfill office area in Hangzhou, China.	0.00	91.20	66	Ying et al., 2012.
Commercial broiler house side wall, Southeastern US.	0.00	84.69	54	Trabue et al., 2010.
Office in non- residential areas	0.00	82.74	53	Chao et al., 2001. Salonen et al., 2009.
Landfill platform in Hangzhou, China.	0.00	82.26	64	Ying et al., 2012.
Tunnel outlet in Hong Kong.	0.00	79.30	102	Ho et al., 2009.
Landfill factory boundary in Hangzhou, China.	0.00	79.09	63	Ying et al., 2012.
House for children with asthma,Detroit, Michingan, USA. (Worst measurement)	0.00	60.15	56	Chin et al., 2014
Tunnel inlet in Hong Kong.	0.00	48.65	102	Ho et al., 2009.
Non-smoking areas in 10 Finnish restaurants.	0.00	42.36	16	Vainiotalo et al., 2008.
Landfill residential area in Hangzhou, China.	0.00	26.63	64	Ying et al., 2012.
Commercial broiler house tunnel area, Southeastern US.	0.00	22.47	53	Trabue et al., 2010.
Nail salon acrylic	0.00	21.49	27	Eklund et al., 2008.

Room, Mall in New Jersey				
Jewelers, Mall in New	0.00	20.11	24	Eklund et al., 2008.
Jersey Home with				, , , , , , , , , , , , , , , , , , ,
Complaints	0.00	16.86	42	Brown, 2002.
Home (average)	0.00	9.12	127	Adgate et al., 2004., Son et al., 2003. Sarigiannis et al., 2011. Billionnet et al., 2011. Guo et al., 2009. Logue et al., 2011.
Home with no complaints	0.00	6.97	41	Brown, 2002.
Stores (average)	0.00	5.66	33	Loh et al., 2006. Eklund et al., 2008.
Teaching hospital in France.	0.00	5.56	33	Bessonneau et al., 2013.
Carlos Pizza Mall in New Jersey	0.00	3.78	31	Eklund et al., 2008.
Outdoors (average)	0.00	2.98	50	Godwin et al., 2007. Adgate et al., 2004. Son et al., 2003. Casello et al., 2009. Brown, 2002
Glen's eye glass store, Mall in New Jersey	0.00	2.14	28	Eklund et al., 2008.
Old homes	0.00	1.97	25	Park et al., 2006.
Personal exposure in Oxford, UK.	0.00	1.78	18	Lai et al., 2004.
Cabin air in car, Summer in Ispra, Italy.	0.00	1.75	20	Geiss et al., 2009.
Bagel World, Mall in New Jersey	0.00	1.72	32	Eklund et al., 2008.
Tickets, Mall in New Jersey	0.00	1.68	26	Eklund et al., 2008.
Workplace in Oxford, UK.	0.00	1.65	13	Lai et al., 2004.
Mixed Greens, Mall in New Jersey	0.00	1.59	27	Eklund et al., 2008.
House Children with asthma in Detroit, Michingan, USA.	0.00	1.48	56	Chin et al., 2014
Inside cars in Birmingham, UK.	0.00	1.45	15	Kim et al., 2001.
Gordon's Corner Deli, Mall in New Jersey	0.00	1.44	31	Eklund et al., 2008.
Paa House Restaurant, Mall in New Jersey	0.00	1.39	32	Eklund et al., 2008.
Tux & Tailor, Mall in New Jersey	0.00	1.33	33	Eklund et al., 2008.
Cabin air in car in	0.00	1.22	20	Geiss et al., 2009.

Ispra, Italy.				
Newspaper stands in			• (G 11 1 2 2000
Bari. Italy.	0.00	1.14	26	Casello et al., 2009.
Non-residential non-				
office Hong Kong	0.00	1.00	9	Chao et al., 2001.
Residential indoor in				
Ovford UK>	0.00	0.96	14	Lai et al., 2004.
Traffician director				
I rafficked roads in	0.00	0.84	13	Kim et al., 2001.
Birmingham, UK.				,
Cabin air in car,	0.00	0.68	20	Geiss et al 2009
Winter in Ispra, Italy.	0.00	0.00	20	Geiss et ui., 2009.
Dry Cleaners, Mall in	0.00	0.65	28	Eklund et al. 2008
New Jersey	0.00	0.05	20	Ekidild et al., 2000.
Video Store, Mall in	0.00	0.40	20	E11 1 (1 2008
New Jersey	0.00	0.49	29	Eklund et al., 2008.
Air cabin bus on				
commercial routes				
Detroit Michigan US	0.00	0.42	14	Batterman et al., 2002.
(Afternoon)				
(Attennoon)				Adapta at al. 2004 Codwin at
School, Michigan, US.	0.00	0.39	27	Augale et al., 2004. Godwill et
				al., 2007.
Pubs in Birmingham,	0.00	0.38	16	Kim et al., 2001.
UK.		0.20	10	
Non-residential	0.00	0.33	9	Sarigiannis et al 2011
indoor. (average)	0.00	0.55	,	
Ambient air, Mall in	0.00	0.21	20	Eldund at al 2008
New Jersey	0.00	0.51	50	Ekiuna et al., 2008.
Air cabin car on				
commercial routes.	0.00	0.21	14	D. //
Detroit, Michigan, US.	0.00	0.31	14	Batterman et al., 2002.
(Afternoon)				
Train station in				
Birmingham UK	0.00	0.30	13	Kim et al., 2001.
Ind home & school in				
Ind nome & school in	0.00	0.20	10	Managla et al. 2010
urban area of La Plata,	0.00	0.26	18	Massolo et al., 2010.
Argentina.				
Buses in Birmingham,	0.00	0.25	13	Kim et al 2001
UK.	0.00	0.20	15	11111 Ct u , 2001.
Department stores in	0.00	0.23	13	Kim et al 2001
Birmingham, UK.	0.00	0.25	15	
Ind home & school in				
industrial area of La	0.00	0.22	18	Massolo et al., 2010.
Plata, Argentina.				
Restaurants in	0.00			
Birmingham UK	0.00	0.22	15	Kim et al., 2001.
Residential outdoor in				
Oxford UK	0.00	0.21	13	Lai et al., 2004.
Dining				
(Smoking & Man	0.00	0.21	16	Loh et al., 2006.
(SHIOKIIIganoli-		1		

smoking)				
Cinemas in	0.00	0.19	13	Kim et al. 2001
Birmingham,UK.	0.00	0.17	15	14iii et ui., 2001.
Train in	0.00	0.18	13	Kim et al., 2001.
Birmingham, UK.				,
Air cabin bus on				
Detroit Michigan US	0.00	0.18	14	Batterman et al., 2002.
(Morning)				
Home suburban/rural				
in New Jersey US	0.00	0.17	19	Weisel et al., 2008.
Libraries in				
Birmingham,UK.	0.00	0.16	13	Kim et al., 2001.
Coach station in	0.00	0.1.6	1.5	
Birmingham,UK.	0.00	0.16	15	Kim et al., 2001.
Ind home & school				
Semi-rural area of La	0.00	0.15	18	Massolo et al., 2010.
Plata, Argentina.				
Ind home & school in				
Residential area of La	0.00	0.14	18	Massolo et al., 2010.
Plata, Argentina.				
Home after cleaning	0.00	0.13	11	Kim et al 2001
in Birmingham,UK.	0.00	0.12		11111 et u , 2001.
Offices in	0.00	0.13	13	Kim et al., 2001.
Birmingham, UK.				
in Dirmingham UK	0.00	0.12	11	Kim et al., 2001.
Homes in				
Birmingham UK	0.00	0.12	15	Kim et al., 2001.
Home after painting		<u> </u>		
in Birmingham,UK.	0.00	0.12	11	Kim et al., 2001.
Air cabin car on				
commercial routes,	0.00	0.11	12	Pattermon et al. 2002
Detroit, Michigan, US.	0.00	0.11	15	Batterman et al., 2002.
(Morning)				
Perfume shop in	0.00	0.11	13	Kim et al 2001
Birmingham,UK.	0.00	0.11	15	Kim et al., 2001.
Smoking homes in	0.00	0.11	13	Kim et al., 2001.
Birmingham, UK.				
Outdoor industrial	0.00	0.00	10	Managha at al. 2010
areas in La Plata,	0.00	0.09	18	Massolo et al., 2010.
Homo hoforo pointing				
in Birmingham LIK	0.00	0.07	11	Kim et al., 2001.
Outdoor in urban areas				
of La Plata Argentina	0.00	0.06	18	Massolo et al., 2010.
Outdoor in	0.00	0.05	1.	W: 1 2001
Birminham, UK.	0.00	0.05		Kim et al., 2001.
Home before cleaning	0.00	0.03	11	Kim et al., 2001.

in Birmingham,UK.				
Bus routes, Pamplona,	0.00	0.02	10	Barro at al 2008
Northern Spain	0.00	0.05	10	Parra et al., 2008.
Laboratories in	0.00	0.02	12	Kim at al. 2001
Birmingham,UK.	0.00	0.02	15	Kim et al., 2001.
Outdoor in semi-rural				
areas in La Plata,	0.00	0.02	18	Massolo et al., 2010.
Argentina.				
Outdoor in residential				
areas in La Plata,	0.00	0.02	18	Massolo et al., 2010.
Argentina.				

Conclusions

Our final Eq. (5) correlates quite a large number of toxicological endpoints for VOCs with SD = 0.63 log units. The VOCs include not only those acting through physical effects but also a range of VOCs that act through specific effects. Eq. (5) covers a wide enough range of VOCs to be able to calculate relative air quality due to VOCs for very many indoor and outdoor environments, as shown by the results in Table 5. However, there are a number of points we can raise that could be addressed in the future.

We showed in the case of ODT values (Abraham et al., 2012) that when log ODT for a homologous series of compounds in one data set were compared to corresponding values of log ODT in another dataset, there was a constant difference between the two sets, and this is the reason why the method of indicator variables works reasonably well. However, it would be useful if exceptions to this 'rule' were identified and treated in a more sophisticated way. There may also be compounds with functional groups that we have not considered, and for which there is sufficient data to test whether they can also be incorporated into our system. One practical constraint is that the descriptors E, S, A, B and L for any compound have to be available before SIT values can be calculated. Although descriptors for a large number of VOCs are available in the literature, there will inevitably be cases where descriptors for particular VOCs have not been determined. These descriptors can be calculated through fragmentation methods (Absolv, 2014) and so there is the possibility that calculational methods could be used to estimate descriptors for any VOC likely to be encountered.

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