

# Interpretation and Limitations of the Concept "Total Volatile Organic Compounds" (TVOC) as an Indicator of Human Responses to Exposures of Volatile Organic Compounds (VOC) in Indoor Air

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## Abstract

*The TVOC summation of masses of non-reactive substances has often been used as a practical way of reporting environmental measurements of volatile organic compounds. This total concentration, moreover, is often used as an indication of the potential of a multicomponent atmospheric pollution with substances of low chemical reactivity to cause chemically induced sensory irritation. This use of the TVOC indicator has never been standardized. Various authors have used different measuring techniques and the results have been used to predict certain types of health effect. This article discusses the toxicological background for the TVOC concept in relation to nonspecific sensory irritation and identifies some theoretical limitations in its use within this context. The TVOC indicator of nonspecific sensory irritations should be based only on a limited range of compounds and should be interpreted as a lower limit of the possible intensity of sensory irritation. Based on the discussions, some precautions are recommended with respect to measurements of TVOC and interpretation of the measurements.*

## KEY WORDS:

Volatile organic compound, Indicator, TVOC, Sensory irritation, Total organic volatiles, TOV.

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## Volatile Organic Compounds (VOC)

A working group of the World Health Organization (WHO) categorized the entire range of organic indoor air pollutants into four groups as indicated in Table 1 (WHO, 1989). No sharp limits exist between the four categories which were defined by boiling-point ranges. The category of volatile organic compounds (VOC) was defined by a boiling-point range with a lower limit between 50 °C and 100 °C and an upper limit between 240 °C and 260 °C (WHO, 1989).

VOC are frequent air pollutants in non-industrial environments. Building- and furniture materials are known to emit VOC (Mølhave, 1986). Ventilation transports outdoor pollutants to the indoor environment and the ventilation system itself may be a source of VOC (Mølhave et al., 1991). Maintenance, cleaning and cooking create their own sources. The human metabolism and human activities such as smoking are sources of gases and vapors. Other sources are photocopying machines, printing machines, glue, spray cans, etc. (Miksch et al., 1982).

The most characteristic features of human activities as sources of VOC are the rapid variation of the emissions over time and the much higher peak concentrations when compared to more steady sources related to building materials or furniture.

Rapidly varying concentrations are easily correlated to variations in the frequency of acute effects such as acute sensory irritation. Such correlations are normally not reported by occupants complaining about acute symptoms related to a deteriorated indoor climate. The average concentrations of compounds emitted from building materials etc. may therefore be more important to the general indoor air quality than the short-lived peak exposures caused by varying sources.

**Table 1** Classification of indoor pollutants<sup>a</sup>

Description	Abbreviation	Boiling-point range (°C) <sup>b</sup>
Very volatile (gaseous) organic compounds	VVOC	< 0 to 50-100
Volatile organic compounds	VOC	50-100 to 240-260
Semivolatile organic compounds	SVOC	240-260 to 380-400
Organic compounds associated with particulate matter or particulate organic matter	POM	> 380

<sup>a</sup> From reference (WHO, 1989)

<sup>b</sup> Polar compounds appear at the higher end of the range.

From a number of early small-scale studies (Mølhave and Møller, 1978; Johansson, 1978; Seifert and Abraham, 1982) it became evident that the concentration of many organic compounds in indoor air exceeds the concentrations in outdoor air. An early literature review dealt with 12 publications on measurements of gases and vapors in the environment (Johansson, 1982). A more recent review lists 307 VOC identified in indoor air in different countries (Berglund et al., 1986).

A WHO report on VOC indoors summarized the concentrations found in four major studies (WHO, 1989). These four studies (Krause et al., 1987; De Bortoli et al., 1986; Lebret et al., 1986; Wallace, 1987) were used to construct one data set for each compound, representative of a typical home. The data set includes percentiles of the concentration distribution for individual compounds.

In summary, 50 to 300 volatile organic compounds (VOC) are typically found in most air samples from non-industrial environments. Each compound seldom exceeds a concentration of about 50  $\mu\text{g}/\text{m}^3$ , which is 100 to 1000 times lower than relevant occupational threshold values (TLV) (ACGIH, 1988). An upper extreme average total concentration of all VOC compounds in normally occupied homes seems to be 20  $\text{mg}/\text{m}^3$  (Mølhave and Møller 1978). The total concentration of all VOC compounds ( $\text{mg}/\text{m}^3$ ), however, is normally well below 1  $\text{mg}/\text{m}^3$ , which is only 0.2% of the TLV for toluene. Toluene is one of the most frequently found compounds in indoor air and it is, in addition, found in relatively high concentrations (WHO, 1989).

## Health Effects Caused by VOC Exposures at Low Levels

### Health Effects

Little is known about the effects of low-level VOC exposures characteristic for non-industrial environments. At high exposure levels they are known to include neurotoxic, carcinogenic, teratogenic and other adverse health effects. Frequent effects of VOC exposure at low levels seem to fall into three categories: a) perception of the environmental exposure caused by acute stimulation of senses (in short, perceived air quality); b) perception or observation of acute or subacute inflammatory-like reactions mostly in the exposed tissues; and finally c) a number of effects which may be classified as a group of subacute environmental stress reactions caused by the perceptions (Mølhave, 1991).

### Perceived Air Quality

VOC are sensed either by the olfactory sense at the top of the nasal cavity, by the gustatory sense on the tongue, or by the common chemical sense (Mølhave, 1991; Cain, 1989). The three sensory systems, mediating the effects of odor, taste and irritation to different degrees, respond to airborne chemicals. Simultaneous stimulation of one or more of these sensory systems seems to result in a combined perception of something the subject calls the perceived indoor air quality. This perceived air quality may include additional signals from other senses such as vision (e.g. haze), or the thermal receptors.

The common chemical sense includes both the trigeminal nerve in facial skin and in mucosal membranes of eyes, nose and mouth as well as non-myelinated nerves in other tissue areas (Cain, 1989). These nerves have polymodal receptors, i.e. they can react to many different types of stimuli. The receptors respond to environmental chemicals either by a chemical reaction with or by a physical adsorption to the receptor proteins. Activation of the senses leads to two effects. First, a sensation of irritation, a burning, smarting or stinging feeling and, secondly, protective reflexes. These may be perceived, for example, as tearing, changed respiratory frequency, cough or sneezing.

### The Exposure Measures

At present, few objective measures are available in relation to indoor air quality, VOC exposures and the relevant covariables. There are two reasons for this: firstly, a relevant measure or unit for the expo-

sure to mixtures of pollutants has not yet been identified and secondly, adequate measuring techniques are lacking.

Analytical procedures for measurements of pollutant concentrations exist for most VOC compounds, but two difficulties often arise when they are used for measurements of low exposure levels. The first is due to the extreme sensitivity of humans to many exposures, e.g. to odorants. This sensitivity is difficult to accommodate with existing technology. Another problem is the many compounds present simultaneously, which make detailed measuring programs time-consuming and expensive.

Three different short-cuts are used to overcome these two difficulties related to measurements of exposure. The first is to use human subjects as detectors, e.g. by means of panels. An example is the olf/decipol theory. This indicator measure has previously been described in the literature (Fanger et al., 1988).

The second short-cut focuses on indicator compounds (such as CO<sub>2</sub> and H<sub>2</sub>O) which are used as indicators for the level of pollution or compounds which in themselves are potent air pollutants (such as CH<sub>2</sub>O). These short-cuts are described in most textbooks on indoor climate.

The last short-cut is focused on calculated indicator measures based on measurable levels of air pollution. One of these indicators is called Total Volatile Organic Compound (TVOC).

In practice, the TVOC indicator originated as a practical way of reporting environmental measurements of volatile organic compounds. Subsequently, it has been used as an indicator of the potency of a pollution to cause health effects. This use of the TVOC indicator has not yet been standardized and various authors are using different definitions. For example, the units of the concentrations included in the TVOC vary and the indicator is used for prediction of different types of health effect. Such inconsistencies limit the interpretive possibilities of the published results. In this review we use known biological mechanisms and physico-chemical properties of non-reactive VOC in a discussion of the relation between TVOC and irritation effects. The discussion is intended to highlight the physico-chemical parameters which are expected to influence most significantly the accuracy of predictions of biological effects from TVOC concentrations. The approximations involved in the TVOC indicator and its limitations can thereby be revealed.

The justification for limiting the discussion to the

non-reactive substances is that many building materials and consumer products emit only non-reactive substances. It is clear that the chemically reactive substances (see Appendix) can be much more potent irritants than the non-reactive substances. Neglecting the higher potency of the chemically reactive substances will lead to an underestimation of the irritancy of a mixture if the estimate is based on the TVOC indicator. On the other hand, if the TVOC indicator suggests that irritation will occur, it is likely that the concentration of VOC will need to be reduced in order to achieve non-irritating indoor air. The TVOC indicator, therefore, can be suggested as a tool for dividing indoor air problems into two groups: problems which can be explained by non-reactive VOC, and those which cannot be explained solely by the concentrations and non-reactive VOC.

### Indicators based on Measured Levels of Air Pollution

For most occupants, symptoms related to perception seem to be the main basis for their evaluation of indoor air quality. The most sensitive organ for such effects is the sensory system directly activated by the exposures (Mølhavé, 1991).

According to our present knowledge, the response of the sensory nerves may be simplified in the following way. The receptors in the thin mucosal membrane are positioned within the mucosa close to the air-mucosa interface. This causes a rapid establishment of equilibrium between air concentrations of chemicals, the concentration of absorbed molecules in mucosa and the activated receptors. A simplified chemical and physical model, therefore, includes three steps which describe the absorption of airborne pollutants into the liquids of the nerves, and the subsequent binding to the receptor which afterwards is followed by an activation of the receptor. The model is described in Nielsen and Bakbo (1985b), Nielsen and Vinggaard (1988a), and Kristiansen and Nielsen (1988a). In the case of sensory irritation, the model assumes, among other things, ideal gas conditions of the air phase and a lipophilic state of the receptor compartment (Nielsen and Alarie, 1982; Nielsen and Yamagiwa, 1989; Nielsen et al., 1990).

The interaction between a physically adsorbed substance and a receptor can be assumed to be a reversible bimolecular reaction:



The ratio between the rate constants  $k'/k'' = K_{eq}$  is termed the affinity constant.

According to the simplest case of the classical receptor theory, the response ( $R_e$ ) is assumed to be proportional to the number of occupied receptors, giving the equation:

$$R_e = \frac{R_{emax} \cdot [S]}{1/K_{eq} + [S]} \quad (2)$$

The maximum response is termed  $R_{emax}$ . The molar concentration  $[S]$  is taken in the receptor compartment. However, only the concentration in the exposure air ( $[S]_{air}$ ) is known. If equilibrium exists, the exposure concentration in the air is related to the concentration in the receptor compartment via the partition coefficient,  $P_{R/A} = [S]/[S]_{air}$ , which, when introduced into Equation 2, gives:

$$R_e = \frac{R_{emax} [S]_{air}}{1/(K_{eq} \cdot P_{R/A}) + [S]_{air}} \quad (3)$$

This equation has been shown to describe the relation between exposure concentrations and sensory irritation (Alarie, 1973; Kristiansen et al., 1986; Kristiansen et al., 1988b; Nielsen and Vinggaard, 1988a; Nielsen et al., 1988b; Nielsen and Yamagiwa, 1989). The apparent dissociation constant  $1/(K_{eq} \cdot P_{R/A})$  is equal to  $[S]_{air}$  for  $R_e = 1/2 \cdot R_{emax}$ . Human exposures both in occupational and in indoor environments are far below the last-mentioned response level (Nielsen et al., 1988b). This is illustrated by the difference between the extreme burning and painful sensation of concentrated ammonia and the much lower irritation found in workplaces and in non-industrial indoor climates. Equation 3, therefore, can be simplified:

$$R_e = \frac{R_{emax} \cdot [S]_{air}}{1/(K_{eq} \cdot P_{R/A})} \quad (4)$$

This equation has the drawback of containing two unknown parameters,  $K_{eq}$  and  $P_{R/A}$ . This can be overcome by applying the activity concept (Brink and Posternak, 1948; Ferguson, 1939).

The molar concentration ( $[S]_{air}$ ) is proportional to the partial pressure ( $P$ ) of the gas. If  $P$  is measured in mmHg and the volume of one mole of a gas (liters) is termed  $V_m$ , the relation becomes:

$$[S]_{air} = \frac{P}{760 \cdot V_m} \quad (5)$$

$V_m$  is a constant which depends only on pressure and temperature. Introduced into Equation 4:

$$R_e = \frac{R_{emax} \cdot P}{760 \cdot V_m \cdot K_{eq} \cdot P_{R/A}} \quad (6)$$

The thermodynamic activity  $a(S)$  of compound  $S$  is defined as the ratio between  $P$  and  $P_0$ , the vapor pressure of the pure liquid (Brink and Posternak, 1948; Ferguson, 1939). Multiplying the numerator and the denominator by  $1/P_0$  gives:

$$\begin{aligned} R_e &= \frac{R_{emax} \cdot P/P_0}{760 \cdot V_m \cdot K_{eq} \cdot P_{R/A} \cdot P_0} = \frac{R_{emax} \cdot a(S)}{760 \cdot V_m \cdot K_{eq} \cdot P_{R/A} \cdot P_0} \\ &= \frac{R_{emax} \cdot a(S)}{K_{act}} \end{aligned} \quad (7)$$

Thus, the apparent activity dissociation constant ( $K_{act}$ ) is related to the conventional mol per liter system by:

$$K_{act} = \frac{760 \cdot V_m}{K_{eq} \cdot P_{R/A} \cdot P_0} \quad (8)$$

An advantage of the activity concept is that the activity is equal in all phases when the phases are in equilibrium. The apparent activity dissociation constant, therefore, can be obtained directly from the exposure concentration. Another advantage is that enough data exist to estimate  $K_{act}$  for different substances belonging to different groups of non-reactive chemicals (see Appendix).

Equation 7 is a simplified expression of a more general equation (Nielsen and Vinggaard, 1988a; Kristiansen and Nielsen, 1988a). In principle, it can be derived in the same way (Nielsen and Vinggaard, 1988a) or obtained directly from the law of mass action expressed by activities (Kristiansen and Nielsen, 1988a):

$$R_e = \frac{R_{emax} \cdot a(S)}{K_{act} + a(S)} \quad (9)$$

Mechanisms of interaction of sensory irritants have been dealt with only to a limited extent. The interaction between two relatively reactive substances, formaldehyde and acrolein, followed that of a com-

**Table 2** The MIX-21 mixture of VOC used for human exposure experiments<sup>a</sup>

Compound	Relative weight
n-Butylacetate	10
2-Xylene	10
n-Hexane	1
n-Nonane	1
n-Decane	1
1-Decene	1
Ethylbenzene	1
n-Hexanal	1
2-Propanol	1
n-Butanol	1
Ethoxyethyl acetate	1
1,2 Dichloro ethane	1
n-Undecane	0,1
Cyclohexane	0,1
1,2,4-Trimethylbenzene	0,1
n-Propylbenzene	0,1
n-Pentanal	0,1
2-Butanone	0,1
3-Methyl-2-butanone	0,1
4-Methyl-2-pentanone	0,1
1-Octene	0,01

<sup>a</sup> Hudnell et al. (1990).

petitive agonism (Kane and Alarie, 1978). This was also the case for the interaction between the two relatively non-reactive substances, cumene (isopropylbenzene) and n-propanol, as long as no desensitization occurred (Nielsen et al., 1988b). Extrapolation to effects expected at occupational threshold concentrations and, therefore, also extrapolation to the even lower indoor air levels, suggested an additive effect. In a recent investigation, interactions between the two sensory irritants, formaldehyde and ammonia, have been investigated in humans. The sensory irritation (pungency) component was found to be mainly additive (Cometto-Muñiz and Cain, 1991b). Accepting this also for a multicomponent mixture and expressing the response by Equation 7 gives:

$$R_e = \sum \frac{R_{emax(i)} \cdot a(S_i)}{K_{act(i)}} \approx \frac{1}{K_{act}} \sum R_{emax(i)} \cdot a(S_i) \quad (10)$$

It is also accepted that  $K_{act}(i)$  is approximately constant (see Appendix). Reintroducing the relation from Equation 5 and the definition of activity in Equation 10 gives:

$$R_e = \frac{1}{K_{act}} \sum R_{emax(i)} \cdot \frac{760 \cdot V_m}{P_o} \cdot [S]_{air} \quad (11)$$

and thus:

$$R_e = \frac{760 \cdot V_m}{K_{act}} \sum \frac{R_{emax(i)} \cdot [S]_{air}}{P_o} \quad (12)$$

Further, the molar concentration  $[S]_{air}$  is equal to the amount of substance in gram (n) per liter divided by the molecular weight (M) in gram. M is approximately constant, e.g. the differences in the molecular weight of the alkylbenzenes in the Appendix (Table 3) deviate by a factor of no more than 2, which is small compared to that of the ratio between the corresponding RD50 values. For the compounds grouped in Table 1 as VOC the range of molecular weights is roughly a factor of 3. The equation therefore is written:

$$R_e = \frac{760 \cdot V_m}{K_{act} \cdot M} \cdot \sum \frac{R_{emax(i)} \cdot n(i)}{P_o} \quad (13)$$

A requirement for reaching an equation where the response is proportional to the sum of mass concentrations is that the ratio  $R_{emax(i)}/P_o$  is constant. For full agonists, e.g. alkylbenzenes mentioned in Table 3, the  $R_{emax}$  is approximately constant. In

**Table 3** Equipotent concentrations of sensory irritants, depressing the respiratory rate by 50% (RD50) in mice, saturated vapor concentrations ("Po") at 37 °C and the thermodynamic activity (RD50/"Po") at the RD50 level

Alkylchain	Alkylbenzenes				Alcohols			
	Substance	RD50(ppm) <sup>a</sup>	"Po" (ppm) <sup>b</sup>	RD50/"Po" <sup>b</sup>	Substance	RD50 (ppm) <sup>c</sup>	"Po" (ppm) <sup>b</sup>	RD50/"Po" <sup>b</sup>
Methyl	Toluene	5300	67000	0.08	Methanol	41500	291000	0.14
Ethyl	Ethylbenzene	4060	24000	0.17	Ethanol	27314	147000	0.19
n-Propyl	Propylbenzene	1530	9200	0.17	Propanol	12704	54500	0.23
n-Butyl	Butylbenzene	710	3300	0.22	Butanol	4784	20200	0.24
n-Pentyl	Amylbenzene	230	1020	0.23	Pentanol	4039	7690	0.53
n-Hexyl	Hexylbenzene	125	359	0.35	-	-	-	-

<sup>a</sup> Nielsen and Alarie (1982).

<sup>b</sup> Nielsen and Bakbo (1985a). Note in this case the "Po" values are the saturated vapor concentration in ppm values, which are proportional to the saturated vapor pressure  $P_o$ .

<sup>c</sup> Kane et al. (1980).

this case the differences in  $P_o$  values seriously affect the possibility of using the mass concentration as an indicator of a biological effect. The importance of  $P_o$  is seen from the fact that  $P_o$  decreases by a factor of 3 (see Table 3), when increasing the alkylchain by a  $-\text{CH}_2-$  group in a homologous series of substances. Fortunately, the alkylbenzenes in the indoor air are generally limited to a few closely related substances such as toluene, ethylbenzene, xylene and cumene (WHO, 1989). Therefore, for this group of substances, the influence of  $P_o$  will not seriously affect the accuracy of the TVOC indicator.

For many other substances the  $R_{\text{cmax}}$  values decrease with increasing length of the alkylchain (as discussed in the Appendix). For these substances the decrease in  $R_{\text{cmax}}$  (i) is "parallel" to the decrease in  $P_o$ . This may also explain the findings of Cometto-Muñiz and Cain (1991a). In determining the nasal pungency thresholds for homologous acetic acid esters and for homologous alcohols (Cometto-Muñiz and Cain, 1990) by a sniff technique using constant dilution steps, they reported: "Spontaneous comments and reactions from the anosmics suggest that when the pungency threshold is reached for the lower members of both homologous series, even one dilution step above it could be overwhelmingly pungent, whereas for the higher members the pungency at threshold is not so effective or clear, so the concentration could be increased by one, two or even three dilution steps above the threshold and no such overwhelming effect is observed. This characteristic is typical of the highest members of both series". Altogether, this suggests that the sum of mass concentrations may be a more accurate expression of the biological effect than could be assumed at first glance if only the  $P_o$  values were taken into account. Nonetheless, the differences in  $P_o$  values should be considered when the mass concentration is used for predicting biological effects of non-reactive substances, as the differences in  $P_o$  may seriously influence the accuracy of the TVOC indicator in the prediction of irritation.

## Discussion

### The TVOC Indicator

At present, no proper unit has been established for a summation of the combined effects of the many different compounds in the atmosphere. Mass addition ( $\text{mg}/\text{m}^3$ ) has been suggested (Møhlhave, 1986; Møhlhave, 1990) in the form of the TVOC indicator. From a biological point of view, the number of mo-

lecules per  $\text{m}^3$  (e.g. in ppm or ppb) may be more relevant. Mathematical functions based on combinations of other variables such as type of radicals, vapor pressure or polarity of the compounds have also been suggested as indicators.

One of the suggested mathematical functions includes the saturated vapor pressure of the pure compound and the partial vapor pressure in the air. The ratio between these pressures is termed the thermodynamic activity and is supposed to be an approximation of the concentration of the pollutant resulting from absorption of the compound from the air into the lipophilic phases surrounding the receptor protein (Nielsen and Alarie, 1982; Nielsen and Bakbo, 1985a; Nielsen et al., 1990). From a toxicological point of view, this is a more relevant exposure measure for nerve tissue than mass concentrations ( $\text{mg}/\text{m}^3$ ) in the air (Ferguson, 1939; Nielsen and Alarie, 1982; Nielsen and Bakbo, 1985a; Kristiansen and Nielsen, 1988a; Nielsen et al., 1990).

In principle, inclusion of more variables such as compound polarity in the function could improve the accuracy of the indicator's prediction of biological effects, but in practice this is impossible because of missing relevant chemical data or the complexity of the resulting mathematical equations. From the theory described above, it appears that the concept of a TVOC indicator is based on the following assumptions:

- The indicator may be related to perceived non-specific stimulation of lipophile nerves. Nonspecific stimulation is a term used for simplicity for effects of non-reactive substances.
- The nerves are supposed to be responding additively to multicomponent air exposure at low levels (e.g. a few ppm or lower).
- The non-reactive compounds must be comparable, especially with respect to molecular weight and apparent activity dissociation constants, and saturated vapor pressure.
- The TVOC indicator cannot be expected to predict other types of effect of substances which react chemically with the receptor, e.g. formaldehyde or acrolein, as discussed in the Appendix.
- The compounds may cause additional specific biological reactions or may deviate strongly with respect to saturated vapor pressure, molecular weight, etc. This may cause an additional irritation. The indicator thus represents, in general, an estimate of the lower limit of irritation.

- Sensory irritation is a nonspecific effect, which may be caused by other environmental factors than VOC, e.g. microorganisms or moulds (Samson, 1985). A significant correlation between TVOC and irritation, consequently, can be expected to exist only when these other factors do not contribute to the prevalence of irritation.

The simplifications used here to derive the TVOC indicator are based on inferences from experimental evidence. However, it must be emphasized that the size of the approximations and the relevance of the concept have not yet been thoroughly tested in practice. At present, this indicator cannot be used for risk assessment, mitigation, etc. Further, co-variables, e.g. in relation to non-chemical exposure and subject sensitivity, have not been investigated in detail, and only a few acceptable measures (or indicators) exist for several of the potential co-variables related to the model.

Previously, some authors have interpreted the TVOC measure only as an indication of risks of nonspecific sensory irritation. Other authors have interpreted the indicator in relation to all types of sensory, or even toxic, effects which may occur in non-industrial indoor environments. Further, the predicted effects have been associated with contributions from effects caused only by the identified compounds included in the summation. Other authors use this summation as an indicator of all compounds present and use the TVOC concept to predict the total effect caused by the identified and unidentified compounds together. It should be borne in mind that the discussion in this paper deals only with the TVOC indicator in relation to one specific health effect (nonspecific sensory irritation) and a specific exposure (VOC compounds with a limited range of vapor pressures).

At present, no theoretical or empirical relation, such as the one discussed here for sensory irritation, has been established for other types of health effect. Consequently, it is speculative whether the indicator may be useful for evaluation of the risks of other types of effect caused by these VOC compounds or for the additional nonspecific sensory irritation caused by other types of exposure than VOC. It is possible that future research may show that the TVOC indicator is useful also in predicting other effects of air pollution or that nonspecific irritation of e.g. SVOC or VVOC can be predicted.

### Health Evaluations of Exposures Indoors to VOC at Low Level

From a previous review of effects caused by low-level exposure to VOC (Mølhave, 1991) and the discussion of the TVOC indicator in this paper, it appears that evaluations of health risks related to low concentrations of VOC must be based on more than the TVOC indicator as this indicator can be expected to indicate only the risk of nonspecific sensory irritation. At present, it appears that at least three different types of health effect must be evaluated separately (Mølhave, 1991). They are:

- *Severe health impacts* such as allergy, cancer or systemic effects (e.g. on the cardiovascular system or the liver). Compounds with high potential for causing these effects must be identified and quantified individually. Compounds without a threshold for effects must be either banned, limited or accepted (e.g. based on evaluations of life-time risks). Traditionally, compounds which have a threshold for effects are evaluated using addition, based on the estimated "no observed adverse effect level" (NOAEL).
- *Nonspecific sensory stimulation*. This type of sensation is considered to be weakest, with a non-odorous effect appearing at lowest concentrations. Future research may show that the lower limit for the thresholds of such effects may be estimated by the TVOC indicator. This indicator is supposed, first of all, to indicate the potential for nonspecific sensory irritation. It is not known whether it predicts any other type of effects caused by the exposure to VOC.
- *Odor*. At present, the risks of odor problems among the occupants cannot be evaluated as no useful models exist for calculation of odor intensity of a mixture of odorants. Therefore, a panel must be used to evaluate the odor intensity. However, also in this case, future investigations may show that the TVOC indicator is useful, as indicated in Figure 1. The figure shows a correlation between FID-measured TVOC and ratings of odor intensity made by a panel using a butanol reference scale (Mølhave et al., 1986). In this case, the correlation was  $r = 0,86$  following a non-linear correlation of  $(\text{mg/m}^3 \text{ butanol}) = 160 \times (\text{mg/m}^3 \text{ FID})^{0,3}$ .

### The Ideal Analytical Measurements of the TVOC Indicator

Traditionally, the VOC summation of masses was used because of its convenience in relation to exist-

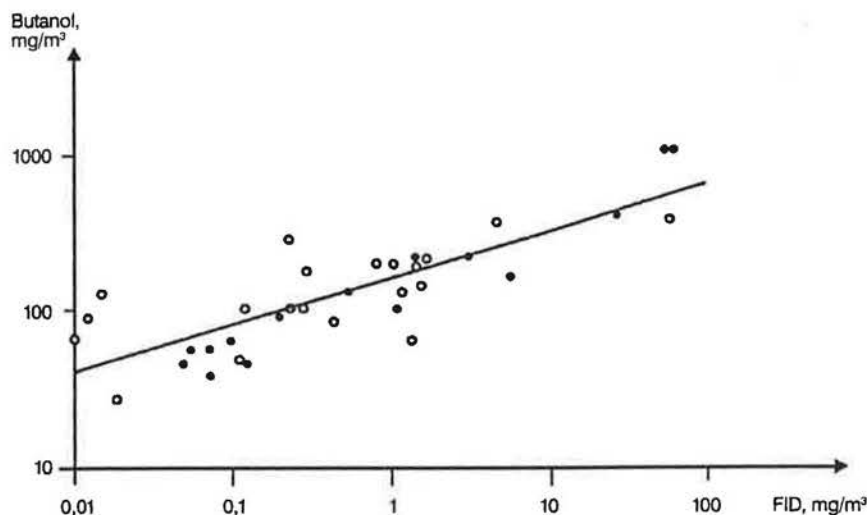


Fig. 1. The correlation between equivalent n-butanol odor intensity and total concentration (TVOC) measured by a FID calibrated against toluene (Mølhave et al., 1986).

ing analytical measuring methods, which allowed easy summation of all compounds identified.

Generally, selection of methods should be based on considerations of quality of results and time and cost considerations. Traditionally, however, measurements of TVOC concentrations have been made with the methods available in each laboratory. Most authors have used their own methods and the reported TVOC summations are indications of "this is what we measure with our technique". Therefore, few reported measurements of TVOC concentrations are comparable.

Generally, the reported analytical methods fall into three classes:

- Direct reading instruments, e.g. a calibrated flame ionization detector (FID) or photo ionization detector (PID).
- Adsorption on a sampling media followed by gas-chromatographic separation of all compounds by one or more columns. In this case, the total concentration may be reported using the total area in gaschromatograms and an average response factor, e.g. of a reference compound (such as toluene).
- Adsorption on sampler and correct quantification of each constituent on MS/GC. In this case, the TVOC is the sum of correctly measured concentrations of all identified compounds. Often the concentrations of unidentified compounds are added in units of a reference compound (e.g. toluene).

These methods all have shortcomings in relation to the toxicological model described above. The model described indicates that the best predicting power

can be expected for a summation of mass concentrations of compounds in a limited range of dissociation constants, molecular weights, and vapor pressures.

The extent to which the TVOC indicator can be used to predict nonspecific irritation of compounds outside these ranges, which have not yet been defined, is still speculative.

Most methods used until now do not specify the ranges of physico-chemical properties of the compounds detected. Further, they apply varying detector response factors for these compounds. Some chemical groups are not seen at all and in some procedures the summation of concentrations is based only on detected compounds, which are further quantified, using an average response factor.

An ideal analytical method must identify and correctly quantify all organic compounds in a specified range of physico-chemical properties. In practice, such procedures in each sample will have to deal with 50 to 300 compounds of all chemical classes. The ideal procedure, therefore, will be very time-consuming and costly, and some short-cuts must be made.

These short-cuts will deal with such analytical difficulties as:

- Definition of the range of physico-chemical properties to include in the summation.
- Simple analytical procedures for identification of compounds belonging to the specified range of properties without a complete identification of each compound.
- Simplified procedures for assigning response factors to each compound.
- How to assess the effects of compounds outside the specified range.



- Calibration and Quality Assurance (QA) procedures.

### The Range of Physico-chemical Properties to include in the Summation

At present, the range of physico-chemical properties to consider for the summation cannot be assessed. Until such information exists, one pragmatic approach would be to standardize the present practice in different laboratories by defining the range in relation to what is seen on normally used gaschromatographic columns. Generally, these procedures are based on boiling points and polarity.

On a unipolar GC-column the average range used by different laboratories for TVOC summations includes VOC compounds with retention times approximately between n-pentane and n-pentadecane. Most authors find this to be the case for the majority of organic compounds with boiling points well above and melting points well below normal room temperature. This range seems to match reasonably well with the WHO definition of VOC (WHO, 1989).

### A Simplified Procedure for Identification of Compounds in the Specified Range

In conclusion, the use of the TVOC indicator should be based on VOC compounds only and should include only a negligible contribution from compounds outside the VOC range. It follows that if this is to be generally adopted in practice, an acceptable method must be able to separate between those groups of compounds described by WHO as very volatile (VVOC), volatile (VOC) and semivolatile compounds (SVOC) (WHO, 1989). This can be achieved by proper selection of sampling media, desorption procedure and gas-chromatographic columns.

Further, it must be ensured that the procedure measures all relevant types of VOC compounds with boiling points within the VOC range and also indicates the presence of the compounds outside the VOC range. Measurements of all relevant compounds may be possible by the use of several columns, including non-polar columns. The performance of the procedures may be demonstrated by measurements of relative recovery of a gasphase reference mixture, which includes all relevant types of VOC compounds. If the WHO definitions of VVOC, VOC, and SVOC are used as a pragmatic example, the TVVOC and TSVOC contribution must be negligible compared to the TVOC contribution.

Therefore, any procedure for evaluation of the TVOC summation must also be able to estimate the fractions outside the VOC range which may be included in the TVOC summation because of reduced selectivity of the procedure.

Generally, such a procedure is not possible using direct reading instruments such as FID or PID. Such instruments, therefore, must be supplemented with other types of analyses to document that the atmosphere in question does not contain major concentrations of compounds outside the VOC group.

### Analytical Response Factors

For practical analytical reasons, response factors cannot be measured routinely for each of the many compounds found in normal indoor air samples. Possible short-cuts include the use of previously measured response factors which are updated occasionally, or the use of average response factors for the whole range of compounds or for segments of the range.

No information exists on which a recommendation of any of these procedures can be made. Until such information is established, a pragmatic standardization would be that the same reference for response is used for all compounds.

Compounds such as toluene or decane have been used routinely as reference for response factors. The rationale for this is that their response factor represents the average response factor for most VOC. Such response factors, however, do not take into account the fact that few air samples contain a full spectrum of VOC or that the selectivity of the sampling and analytical procedure may lead to loss of polar or reactive compounds, which often have strongly deviating response factors.

If average response factors are used in a simplified procedure (e.g. direct FID measurements (Gammage, 1986)), an acceptable correlation between the results of this procedure and detailed quantifications must be demonstrated, e.g. by use of a reference mixture.

Very little has been done to correlate TVOC results obtained by different analytical methods. Figure 2 from Mølhave et al. (1986) shows an example of a correlation between direct FID measurements and measurements including charcoal sampling and subsequent quantification on gaschromatograph and massspectrometer. In this case, the correlation based on the generic equation:  $FID = b \times (\text{Charcoal})^a$  was found to be  $a = 0,75$  with  $r = 0,986$ .

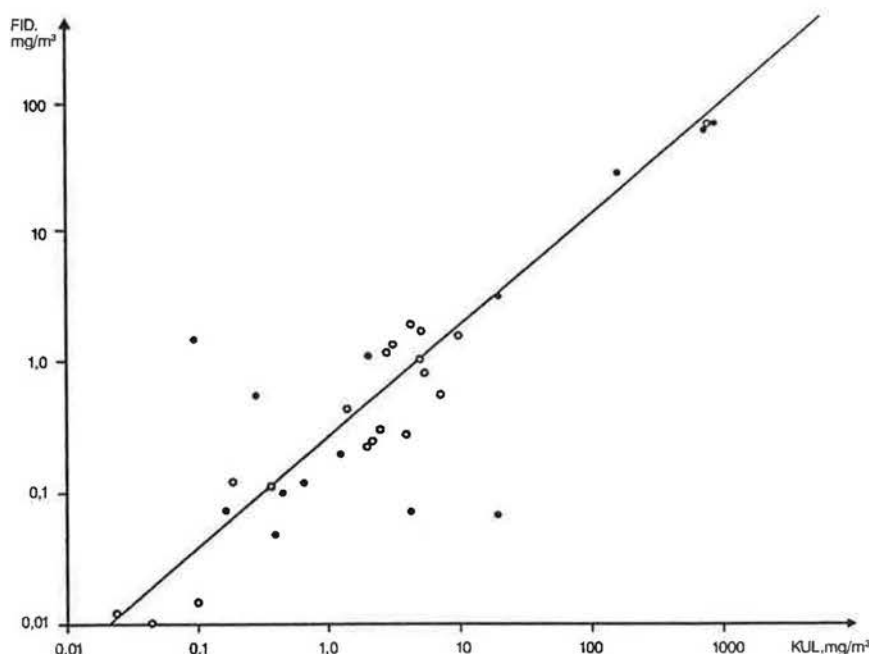


Fig. 2. Correlation between FID-measured TVOC and TVOC concentration obtained from charcoal sampling followed by GC/MS quantification (Mølhave et al., 1986).

### Compounds Outside the Specified Range

The toxicological model described previously in this paper does not predict that the TVOC measure can be used for compounds outside an as yet unspecified range. However, it is reasonable to expect that similar indicators based on the same principles may be defined in other ranges of physico-chemical properties. At present such ranges cannot be defined based on scientific data. If the toxicological model for these ranges proves similar to the TVOC model described previously, then for sufficiently narrow ranges of vapor pressure, etc., these models will predict that the average potential of compounds in these ranges and the total effect of compounds from all ranges may be estimated using weight factors for each range.

If as an illustration, the WHO definition of organic air pollutants is used (WHO, 1989), then indices for Total Very Volatile Organic Compounds (TVVOC) and for Total Semivolatile Organic Compounds (TSVOC) may be defined and the total potential of all organic vapors (TOV) in a mixed air pollution evaluated through the sum of these and the TVOC, using weight factors. It should be stressed that these terms and the ranges for their summations are completely speculative. The TOV indicator of the relative potential of a mixed pollution to cause nonspecific sensory irritation then takes the (speculative) form:

$$\text{TOV} = W_1 \times \text{TVVOC} + W_2 \times \text{TVOC} + W_3 \times \text{TSVOC}$$

where  $W_1$ ,  $W_2$ , and  $W_3$  are yet undefined constants or weight factors.

Until more information is available, a standardization of existing procedures would include the assumption that the weight factors  $W_i$  are equal to one. Such an assumption may be reasonable if the TVVOC and TSVOC fractions are small compared to the TVOC fraction.

### Calibration and QA Procedures

The general conclusion from the previous discussion is that practical TVOC measurements should be made by correct quantification of as many compounds as possible on several columns, including non-polar columns. The concentration of unidentified compounds should be estimated based on a reference compound (or possibly on an average response factor of a mixture of compounds). The relative contribution to the summation of compounds outside the VOC range should be demonstrated to be negligible.

The selectivity of the methods and sampling procedure inside and outside the range must be demonstrated by measurements of relative response factors of the reference mixture.

Simplified procedures, such as FID-detectors, may be used for routine measurements of atmo-

spheres of only slightly varying composition if for each type of atmosphere an acceptable correlation is established to measurements based on correct quantification.

If the WHO definitions of VVOC, VOC and SVOC are used for a pragmatic separation of the ranges, the calibration and QA procedures for the suggested standardized pragmatic measurement of a TOV indicator include documentation of:

- The relative sensitivity of analytical procedures in the three ranges of compounds VVOC, VOC and SVOC to all relevant types of chemicals.
- The absolute response factor of a reference compound.
- How much of the total mass of pollutants is found between and outside the marker compounds for the limits between the ranges of vapor pressure.

No reference mixture exists for measurements of sensitivity. If one is agreed upon, the best guess at present is that it should contain compounds with the following characteristics:

- Compounds belonging to the three ranges of boiling points (BP) below 50/100 °C, between 50/100 °C and 240/260 °C, and above 240/260 °C where the higher values refer to polar compounds.
- Compounds in each range representing all chemical classes normally found in non-industrial indoor environments including polar and non-polar compounds and in concentrations reflecting normal indoor environments.
- For safety reasons, only compounds without severe health risks can be used.

Such a mixture has not yet been generally agreed upon. However, for several years a similar mixture has been used for human exposure experiments and Table 2 shows a recently used version of this mixture (Hudnell et al., 1990). This mixture does not fulfil all three criteria suggested above. However, until another mixture has been established, this mixture of VOC compounds may be used in a generator as described in Hudnell et al. (1990) to calibrate the TOV measurements.

## Summary

The TVOC summation of masses of non-reactive substances has often been used as a practical way of reporting environmental measurements of volatile

organic compounds. This total concentration, moreover, is often used as an indication of the potential of a multicomponent atmospheric pollution with substances of low chemical reactivity to cause chemically induced sensory irritation. This use of the TVOC indicator has never been standardized. Various authors have used different measuring techniques and the results have been used to predict certain types of health effect. This article discusses the toxicological background for the TVOC concept in relation to nonspecific sensory irritation and identifies some theoretical limitations in its use within this context. The TVOC indicator of nonspecific sensory irritations should be based only on a limited range of compounds and should be interpreted as a lower limit of the possible intensity of sensory irritation. Based on the discussions, some precautions are recommended with respect to measurements of TVOC and interpretation of the measurements. It is suggested that the quality of TVOC measurements in practice should be better documented. The measurements may be made in two ways. The first procedure is based on a correct quantification of as many compounds as possible and addition of the estimated concentrations of unidentified compounds. If initial detailed analyses indicate that the atmosphere has only slightly varying compositions from time to time, a simplified procedure may be used for routine measurements. In such cases an acceptable correlation must be established between the simplified measurements and those based on correct and detailed quantification.

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## Appendix

Equation 9 can be rearranged to:

$$a(S) = \frac{R_e}{R_{emax} - R_e} \cdot K_{act}$$

Thus, if comparing substances at the same fraction of the maximum response,  $a(S)$  is proportional to  $K_{act}$ . Table 3 shows the equipotent concentrations of alkylbenzenes depressing the respiratory rate in mice by 50% (RD50) due to a trigeminal effect (Nielsen and Alarie, 1982). Alkylbenzenes have approximately the same maximum response, seen

from the nearly identical slopes of the concentration-response curves. The equipotent concentrations, therefore, can be used directly for comparison. It will be seen that the activities are almost constant (deviate by a factor of 4) if compared to the much broader range of the RD50's. A comparison of alkylbenzenes, halogenated benzenes and halogenated alkylbenzenes shows likewise that the activities are approximately equal (Nielsen et al., 1990; Nielsen, 1991).

In mice, alcohols gave the same type of results (Table 3), which is in agreement with another investigation carried out by de Ceaurriz and co-workers (for details see Nielsen and Bakbo, 1985a). Electrophysiological investigations of trigeminal effects have been carried out in rats (Silver et al., 1986). The activity at the equipotent concentrations varied much less than the corresponding exposure concentrations. For alcohols it is important to realize, however, that the maximum responses decrease by increasing the length of the alkylchain, seen both from the electrophysiological results (Silver et al., 1986) as well as from a comparison of results obtained by the reflex method (Kristiansen et al., 1986; Kristiansen et al., 1988b). The activities corresponding to the thresholds of detection of alcohols in anosmic subjects (detection through the trigeminal system) showed that the activities were virtually equal (Cometto-Muñiz and Cain, 1990). The data from both the electrophysiological test and from the human sniff test were correctly compared at the same (zero) fraction of the maximum responses.

In Table 3, the mean activity of alkylbenzenes and alcohols is equal to 0.23 and the activities thus deviate from this value by a factor of less than three. This suggests that accepting  $K_{act}$  as a constant for non-reactive substances will have only a limited influence on the validity of the deviation.

A recent investigation by Cometto-Muñiz and Cain (1991a) determined the nasal pungency and eye irritation thresholds for homologous acetic acid esters. When expressed as thermodynamic activity, both types of threshold were remarkably constant within the homologous series.

The activities corresponding to those of the range of the concentration-response curves for different alkanes were also found within the same range (Kristiansen and Nielsen, 1988a) and the ranges were furthermore within those of alkylbenzenes and alcohols. For alkanes a marked decrease in maximum responses was seen when the length of the hydrocarbon chain increased (Kristiansen and Nielsen, 1988a).

Altogether, a fair amount of data suggests that the  $K_{act}$  values are approximately equal for the non-reactive substances, e.g. alkylbenzenes and alcohols. This should be compared with the values of chemically reactive substances as illustrated by the RD50 for propanol, given in Table 3, and the RD50 (3.9 ppm) for the corresponding chemically reactive allyl alcohol (Nielsen et al., 1984). The corresponding activities are 0.23 and  $5.9 \cdot 10^{-5}$ . This indicates that the differences in  $K_{act}$  vary by a factor of  $0.23/(5.9 \cdot 10^{-5}) = 3.9 \cdot 10^3$ , assuming equal maximum responses. The saturated vapor concentration of propanol and allyl alcohol is 55500 and 66000 ppm, respectively, at 37 °C (Nielsen et al., 1984), indicating that the two Po values are of the same size. The two substances both contain an alcohol group and have virtually the same volume. Although a small difference exists, one molecule contains a saturated C-C bond whereas the other contains a C=C double bond, which probably has little effect on the partition coefficient. Thus, the ratio according to Equation 8 reflects also the difference in the affinities in the mol/l system. The ratio between the activities is also close to the ratio of the RD50's,  $12704/3.9 = 3,3 \cdot 10^3$ . The difference between the  $K_{act}$  for chemically reactive and for non-reactive substances can clearly vary tremendously simply due to differences in chemical reactivity. This difference, however, will not be dealt with in this report.

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