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Volatile Organic Compounds, Indoor Air Quality and Health

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Abstract

This publication summarizes field investigations and controlled experiments on the relation between low levels of indoor air pollution with volatile organic compounds (VOC) and human health and comfort. The Henle-Kock criteria from epidemiology are revised for the dose-response relation between VOC's and health as comfort effects and existing evidence for each criterion are discussed. A biological model for human responses is suggested, based on three mechanisms: sensory perception of the environment, weak inflammatory reactions, and environmental stress reactions. Further, the TVOC-indicator concept for exposure is discussed. The conclusion is that no experimental or field data contradict the proposed causality. On the contrary, evidence supports the suggested causality. The biological model, however, is not yet based on acceptable measures of the variables for exposures, co-variables or health effects. A tentative guideline for VOC's in non-industrial indoor environments is suggested. The no-effect level seems to be about 0.2 mg/m³. A multifactorial exposure range may exist between 0.2 and 3 mg/m³. Above 3 mg/m³ discomfort is expected.

KEY WORDS:
Health, Comfort, Perceived indoor air quality, Environmental stress, TVOC, Volatile organic compounds.

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Introduction

Volatile Organic Compounds and Health

Volatile organic compounds (VOC's): VOC's are frequent air pollutants in non-industrial environments. A WHO working group categorized the entire range of organic indoor pollutants into four groups, as indicated in Table 1. The four categories were defined by boiling-point ranges and no sharp limits exist between them. The VOC category 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, where the higher values refer to polar compounds (WHO, 1989).

A recent review lists 307 VOC's identified in indoor air in different countries (Berglund et al., 1986). The WHO report (WHO, 1989) on VOC's indoor summarized the concentrations found in four major European studies (Krause et al., 1987; De Bortoli et al., 1986; Lebret et al., 1986; Wallace, 1987). In summary, normally 50 to 300 volatile organic compounds are found in air samples from most non-industrial environments. Each compound seldom exceeds a concentration of about 50 μg/m³, which is 100 to 1000 times lower than relevant occupational threshold values (TLV's) (ACGIH, 1988). An upper extreme average total concentration of all VOC's in normal homes seems to be 20 mg/m³ (Mølhave, 1986). The total concentration of all VOC's (mg/m³), however, is normally well below 1 mg/m³, which is only 0.2% of the occupational threshold limit value (TLV) for toluene.

Table 1 Classification of indoor organic pollutants [a].

Description	Abbreviation	Boiling-point range (°C)[b]
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

[a] From WHO 1989.
[b] Polar compounds appear at the higher end of the range.

Health

Health has been defined by WHO as "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 1961). The toxic effects of volatile organic compounds may be defined as any significant change caused by VOC's on a person when compared to otherwise comparable, but unexposed persons. Such effects may be classified in effects common to most VOC's and effects specific for individual compounds.

The special properties of individual compounds may result in unusually high intensity or prevalence of common effects (such as neurotoxic effects, cancer, or allergy). Many of the special effects are not caused by the air pollutants themselves, but by e.g. metabolites as in the case of the neurotoxicity of n-hexane and certain ketones, the ocular toxicity of methanol, or the hepatoxicity of certain chlorinated hydrocarbons. A list of special effects of VOC's and commonly used tests for such effects are shown in Table 2, which is adapted from Andrews et al. (1986). This table lists effects or tests commonly used in human studies of normal industrial organic solvents at or above TLV-levels. Reviews of such special effects are found in textbooks.

Special effects like genotoxic effects or effects on the immune system are severe for the few unlucky occupants affected by them.

Table 2 Symptomatology and commonly used tests for behavioral effects caused by VOC[a].

Symptomatology	Test
Sensory: Parasthesias, visual or auditory defícts	Neurologic, sight, and hearing examinations
Cognitive: Memory (both short-term and long-term), confusion, disorientation	Wechsler Memory Scale Wechsler Adult Intelligence Scale (WAIS)
Affective: Nervousness, irritability depression, apathy, compulsive behavior	Eysenck Personality Inventory Rorschach Test Digit-symbol Substitution Task Bourdon-Wiersma Vigilance Task
Motor: Weakness in hands, incoordination, fatigue, tremor	Neurologic examination Santa Ana Dexterity Test Finger-tapping Test Simple or Choice Reaction Time

[a] Andrews et al., 1980.

They are, compared to what we know, rare effects in relation to low-level VOC exposures in normal indoor environments. Such effects, however, may evade registration if their prevalence is too small to cause a statistically significant association in a population of the size found in most normal non-industrial buildings. In the future, they should be investigated further.

This paper is focused on the causality behind the more common effects of VOC's according to the above definition. These also happen to be the most frequent effects of low-level VOC exposure. For simplicity, the effects of low-level exposures to VOC's will be divided into a) disturbances of body functions and b) perception of the environment or of body conditions. Further, to avoid confusion, the term *perceived indoor air quality (PIAQ)* will be used for the subjectively perceived air quality in contrast to *measured indoor air quality (MIAQ)* which is the chemically or physically measured indoor air quality, e.g. in the form of air temperature, air humidity, pollution concentrations, etc. A distinction will be made between the occupants' adapted perception after exposure for 1 hour or more and the visitors' immediate and adapted response upon entering the room. Generally, in this paper these two types of evaluation are referred to as subacute and acute responses. Also, the term "irritation" will be specified as either stimulation of sensory systems, inflammatory-like skin reactions, or a psychologic mood condition. If not specified, sensory irritation is meant.

Criteria for Causality

Tables 3 and 4 show a suggested set of criteria for causality and for biologically reasonable etiologies in relation to VOC exposures at low levels and health effects as they may occur in non-industrial indoor environments. In epidemiology, the criteria in Tables 3 and 4 are known as the Henle-Kock-criteria (Evans, 1976). The Henle-Kock criteria originally were developed for the causality of diseases described by a spectrum of responses and caused by specific agents. These criteria have been revised in this paper for

Table 3 Henle-Kock-criteria for causation revised for the effects of low-level VOC exposure among occupants of non-industrial indoor environments[a].

1) A spectrum of responses should follow exposure to VOC's along a predicted *biological gradient* from mild to severe.
2) A *measurable response* following exposure to VOC's should regularly appear among occupants lacking this before exposure or should increase in magnitude if present before exposure.
3) *Exposure to VOC's* should be present more commonly in those showing the effect than in controls without the effect when all risk factors are held constant.
4) *Temporality:* The effects should follow exposure to VOC's (possibly with a delay time).
5) *Elimination of modification* of the VOC exposure or prevention or modification of the occupants' sensitivity to exposure should decrease or eliminate the effect.
6) *Experimental reproduction* of the effects should produce higher incidence in animals or humans appropriately exposed to VOC's than in those not so exposed.
7) The etiology must make *biological sense.*

[a] Evans 1976.

Table 4 Four criteria for acceptable biological explanation of the etiology between low-level VOC exposure and observed effects[a].

1) Reasonable and documented biological mechanism, must be used for the explanation of the observed symptoms or effects.
2) The variables (effects, exposures and cofactors) involved in the suggested etiology must be measurable: alternatively acceptable indicators must be available.
3) The effects or symptoms and expected mechanisms should preferably be known from similar or higher exposure levels to VOC's.
4) The etiology must explain any delay (latency) in responses following exposure to VOC's.

[a] Evans 1976.

the causality relation between VOC's and indoor air quality (IAQ).

Biological Model for Health Effects caused by VOC Exposures at Low Levels

The Background for a Biological Model of Human Reactions to Low-level Exposure to VOC's

One of the Henle-Kock criteria in Table 3 for a causality between VOC's and health effects (e.g. complaints about reduced indoor air quality) was that a reasonable biological model exists which can explain the known features of the suggested causality. In the following, such a model will be suggested with the aim of explaining as many as possible of the indications found in the literature and leaving a minimum of unexplained evidence of effects. The suggested model is still a postulate and should be challenged in future experiments and investigations.

Little is known about the effects of the low-level VOC exposures, which are characteristic of non-industrial environments. Evidence from experiments and investigations indicates that, generally, the responding tissues are mucosal membranes in eyes, nose and throat, skin on the face, neck and hands, and the upper and lower airways (Mølhave, 1986). The most frequent effects seem to be consequences of reactions close to the surface of the tissue exposed to air. Generally, the effects are reversible and disappear shortly after the exposure is ended (Mølhave, 1986; Mølhave, 1990a; Mølhave, 1991a).

The most frequent effects seem to be acute. They may, like perception of odors, show adaptation (Clausen et al., 1985). Some effects may be sub-acute in which case they, like headache, are expected to increase in frequency and intensity with increasing exposure time (Otto et al., 1990; Mølhave, 1990a).

The acute effects appear to fall into three classes (Cain, 1989; Cain et al., 1986; Cometto-Muniz et al., 1984; Medina et al., 1982): The first class contains the primary perceived stimulation of the sensory system caused by the air pollution. Especially olfaction and the trigeminal nerve seem to be involved in these reactions. The second class includes effects related to changes of the skin or other exposed tissue. These effects are either directly caused by the exposure or secondarily caused by perception of changes in the tissues. Such changes may be mediated by nervous or biochemical reflexes. The third class includes observable changes in human behavior (Cain, 1989).

The sub-acute effects are observed (Mølhave, 1986) as headache and other weak subjective nervous-related effects or weak inflammatory-like reactions. Chronic effects like systemic, genotoxic or immune-system effects caused by absorbed or metabolized VOC's are not frequent consequences of low-level VOC-exposures (Mølhave, 1986).

A Biological Model of Human Reactions to Low-Level VOC Exposures

From the evidence summarized above, it appears that the most frequent acute or subacute effects of VOC exposure at a low level fall into three main classes: a) perception of the environmental exposure caused by acute stimulations of senses, b) perception or observation of weak acute or subacute inflammatory-like reactions in the exposed tissues, and finally c) a number of effects which may be described as a group of subacute environmental stress reactions caused by the perceptions (Mølhave, 1990b).

Perceived air quality: Our present knowledge about the senses indicates that VOC's are sensed by either the odorous sense in the top of the nasal cavity, the gustatory senses on the tongue or the chemical sense (Cain, 1989). The three sensory systems – odor, taste and chemical sense – respond to airborne chemicals, but to different qualities of the exposure. Stimulation of one, two or three of these sensory systems seems to result in a combined perception of something which may be called the perceived indoor air quality (PIAQ). This perceived air quality may even include additional nerve signals from other senses like vision (e.g. haze), or the thermal environment.

The chemical sense includes both the trigeminal nerve in facial skin and in mucosal membranes of eyes, nose and mouth, as well as other similar non-myelinated nerves in other skin areas (Cain, 1989). These nerves have polymodal receptors. They, therefore, can respond to many different types of stimuli. The receptors are supposed to respond to environmental chemicals following a chemical reaction or a physical adsorption of the compounds to the receptor proteins.

Activation of the senses leads to two effects. First, a sensation of, for example, an irritation, a burning, smarting or stinging feeling and, secondly, protective reflexes. These may, for example, be tearing, changed respiratory frequency, cough or sneezing (Brink et al., 1948; Nielsen et al., 1985a; Nielsen et al., 1988).

At low-level exposures the common chemical sense exhibits some spatial summations i.e. the more tissue and sensors exposed the stronger is the perceived irritation (Cain, 1989). Time summation also seems to appear at least over short-time exposure of a duration of seconds (Cometto-Muniz et al., 1984) or minutes (Cain et al., 1986). Adaptation may appear at high exposure levels, but time summation for exposures of hours' duration has not been investigated in detail. A summary of the chemical sense is found in Cain (1989) which discusses some of the possible mechanisms behind summation and adaptation.

Inflammation: In medicine, inflammatory reactions are related to microbiologic, metabolic or immune system reactions and are generally considered to be a protective reaction to a potential cell damage. Inflammation is known both as acute and subacute reactions (Thaysen et al., 1980). Only the acute reversible reactions seem to be relevant to the low-level VOC exposures in non-industrial environments. Generally, the first sign of acute inflammation is indications of peripheral dilatation of vessels causing color and temperature changes of tissue. Subsequently granulocytes and other cell types are activated (Thaysen et al., 1980).

Most acute inflammatory reactions are supposed to be activated by chemical mediators released in the exposed tissues. More than ten different chemical classes of mediators have been identified (like histamine and kinines). These mediators are produced after an external exposure to irritants. Most of these mediators are themselves known to be sensory irritants and are believed to stimulate sensors in the tissue and cause a secondary perception of the exposure (Thaysen et al., 1980).

If the exposure increases in intensity or duration beyond the point of comfort or safety, the body may react by initiating protective reflexes or mechanisms. These reflexes may be activated either by chemical mediators or through sensory perception and nervous signals. Examples are running eyes or nose, cough, changes in respiratory pattern, increased mucosal secretion, increased blood flow to exposed skin areas, etc.

Environmental stress: The constant effort needed to identify the wanted and to override the unwanted sensory information, as well as the efforts needed to maintain protective reflexes, is a strain to humans and may by itself cause secondary effects. If such stress situations are continued for an extended period of time, stress-like complaints will arise, of which headache seems to be the most important.

Symptoms of weak environmental stress are well known from both the indoor and the outdoor environment. Many different physical or chemical exposures have been shown to cause these typical stress symptoms which have been reviewed by Evans et al. (1989). Some typical symptoms are shown in Table 5.

Table 5 Some typical symptoms of environmental stress[a].

Increase in stress hormone levels.
Blood pressure increase.
Fatigue.
Irritability and reduced tolerance.
Reduced productivity, errors.
Psychological symptoms.
Attempts to change stressors.
Feeling of helplessness, lack of control of stressors.
Changes in feeling of job satisfaction, or life quality.

[a] Evans et al. 1989.

Figure 1 shows a biological model, which may explain the combined reactions of humans to multifactorial exposures in the indoor environment (MIAQ) including VOC's. Most environmental exposures or stressors cause overlapping spectra of health effects. According to the model, the combined reversible effects of a MIAQ exposure which include a major VOC component fall into the three classes described above. They are: perception, inflammatory-like and stress-like reactions.

In the exposed tissue both primary and secondary acute processes occur. The primary processes are stimulation of sensory nerve endings or initiation of weak inflammatory tissue reactions. The secondary acute effects in the exposed tissue are perceptions of the tissue reactions, initiated reflexes due to the primary perception of exposures, or changed sensitivity of the senses due to tissue changes. Subacute effects may also occur. They are environmental stress reactions or more severe skin reactions. The three types of effect expected to follow from low-level exposure to VOC according to this model are summarized in Table 6.

The intensity of each of the symptoms may be modified by additional factors such as age, smoking history, or gender. Further, the number of symptoms observed and their intensity may cause a feedback on the individual's behavior, thereby causing them, for example, to modify their environment, or to focus on certain symptoms and thus suppress others. Consequently, each subject may react differently to the mixed exposure and exhibit only a few of the symptoms from the spectrum of symptoms observed in the exposed population as a group.

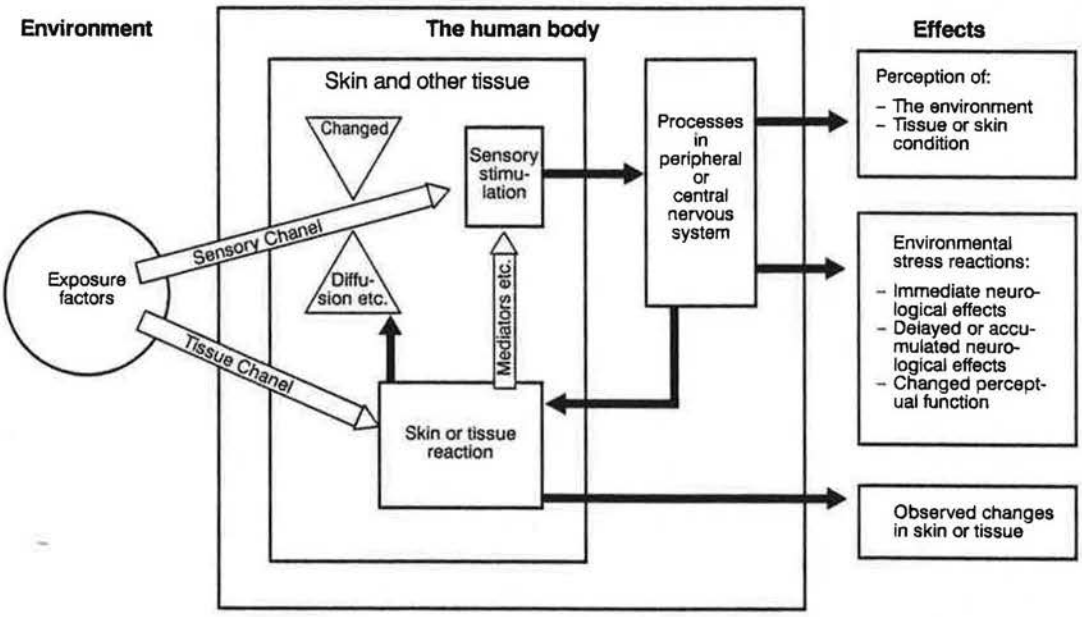

Fig. 1 A biological model for human responses to exposures to low levels of mixtures of volatile organic compounds (VOC's) as air pollution in non-industrial indoor environments.

In this model, the type of effects associated with VOC exposures are unspecific and may be caused by environmental exposures other than chemicals. For example, physical exposures, such as temperature or inert dust, may cause a similar spectrum of symptoms. Any discussion of a causality between VOC's and the type of symptoms appearing in Table 6, therefore, must discuss not only the VOC exposure levels but also the level of other contributing exposure factors.

The discussions in occupational hygiene normally focus on one health risk factor at a time and in such ranges of it that the considered exposure factor can be assumed to be the only, or at least the primary, cause of health effects. Such extreme exposures are typically not found in non-industrial buildings. In consequence, the dose-response relationship may be multifactorial and include a number of exposure factors (temperature, concentration of pollutants, etc.) in the etiology.

Under field conditions, three exposure ranges are of interest. They are defined by the relative contribution of VOC exposure to the prevalence of effects or symptoms. Below a lower threshold (the no-effect level) no effects are expected to follow from the exposure to VOC's despite any other simultaneously occurring exposure. Above an upper threshold (the effect level), an effect of VOC's is expected even when all other exposure factors are controlled and acceptable.

Between the two thresholds a correlation may or may not occur between VOC's exposure and the prevalence of effects, depending on the interactions from other exposure factors or the composition of the exposure. This range is called the multifactorial exposure range. In this exposure range a consistent or monotonous dose-response relationship may not exist and complaints may not necessarily disappear if one of the relevant exposure factors is removed from the environment.

The Exposure Measures of the Model

At present, few methods are available for objective measurements (MIAQ) of VOC exposures and co-factors. Measuring techniques exist for the concentrations of most VOC's, but two problems often prevent the use of these methods at low exposure levels. The first is the extreme sensitivity of humans to many types of exposure, e.g. to odorants. This sensitivity is difficult to match with existing measuring techniques. Another problem is the many compounds present at the same time which make any detailed measuring program 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. as panels. An example of this is the olf/decipol theory. This indicator measure is described elsewhere (Fanger et al., 1988). The idea is to quantify pollution sources in buildings by comparing them to a well-known pollution source. The unit for the emission rate of bio-effluents (air pollutants) is taken to be the emission from a standard person in thermal comfort. The unit is called an olf. One olf is the perceived air pollution caused by one standard person ventilated by 10 l/s of unpolluted air. Other sources, therefore, are quantified by the number of standard persons (olfs) required to cause the same dissatisfaction (which is expressed in decipol) as the actual pollution source. Given a certain percentage of dissatisfied among a panel of judges, the number of standard persons (olfs) that would cause the same dissatisfaction can be calculated. This number is the olf value of the pollution source. The olf value is not supposed to provide information on possible health risks of the pollution source other than the perceived air quality. The value refers to the visitors' situation and not to that of the occupants.

The second short-cut focuses on tracer compounds which are used as indicators for

Table 6 Three classes of human responses to VOC's in normal indoor air. Primary reactions are observed at acute low-level exposures. Secondary effects are observed after prolonged or more intense exposures. Their intensity depends on the properties of the dominating compounds in the exposures and on the sensitivity of the subjects. The table further shows examples of effects found in controlled experiments with humans.

A: Acutely perceived deterioration of the quality of the environment.

	Type of mechanism	Examples of effect	Concentration (mg/m³)					
			3	5	8	15	25	40
Primary	Recognition of exposures	Odor perception	+2	+1	0	0	+4 +5	+3
		Stinging, itching etc.	0	(-1)	+2	0	+4 +5	+3
		Reduced air quality, Need more ventilation	0	0	+2	0	+1 +4 +5	+3
Secondary	Reflexes in eyes, nose and airways	0	0	0	0	0	0	0
	Changed mucosal secretion	Changed tearfilm stability	0	0	0	0	0	+3
		Changed cell counts in eye liquids	0	0	0	0	+4	+3
	Difficulties in breathing	0	0	0	0	0	0	0
	Activities to change the environment	Need more ventilation	0	0	+2	0	0	0

B: Acute or subacute reactions in skin or mucous membranes similar to beginning inflammatory reactions.

	Type of mechanism	Examples of effect	Concentration (mg/m³)					
			3	5	8	15	25	40
Primary	Dilation of peripheral vessels	0	0	0	0	0	0	0
	Stinging, itching or tingling feeling	Perceived irritation	0	(-1)	+2	0	+5	+3
Secondary	Pain	0	0	0	0	0	0	0
	Changed skin temperature	Perceived skin temperature	0	0	0	0	(+1)	0

C: Subacute and weak stress-like reactions ("Environment stress").

	Type of mechanism	Examples of effect	Concentration (mg/m³) 3	5	8	15	25	40
Primary	Discomfort and complaints	Headache	0	0	0	-2	-1 -4 +5	0
		Drowsiness	0	0	0	0	+5	0
Secondary	Complications in body functions and physiological effects	Changed composition of eye and nose liquids	0	0	0	0	(+1)	0
		Changed odor threshold	0	0	0	0	(+1)	0
		Changed performance	0	0	0	0	(+1) (+4) -5	0
		Changed mood	0	0	0	0	(+1) +5	0
		Changed lung function	0	0	0	0	(+4)	0

+ Significant effect.
- No effect seen.
0 No information.
() Indication of effect/no effect.

References:
1. Mølhave et al., 1986
2. Mølhave et al., 1990
3. Kjærgaard et al., 1989
4. Kjærgaard et al., 1991
5. Otto et al., 1990.

the level of pollution, such as carbon dioxide (CO_2) and water (H_2O), or compounds which themselves are potent air pollutants, such as formaldehyde (CH_2O). This short-cut is described in most textbooks on indoor climate. The third and last short-cut focuses on indicator measures of the total measurable level of air pollution. One of these indicators is called Total Volatile Organic Compound (TVOC), and is discussed in Mølhave et al. (1992).

The Concept of Total Volatile Organic Compounds (TVOC)

At present, no proper measuring unit has been established for the combined effects of the many different compounds in the atmosphere. Addition in mg/m³ of masses of polluting molecules has been suggested and in relation to volatile organic compounds it is often called the TVOC indicator (Mølhave, 1986, 1990b). This measure is easily obtained through the chemical analysis (e.g. using an integrating FID detector). From a biological point of view, number as molecules per m³ (the molar concentrations in PPM or PPB) may be more relevant. Mathematical functions based on combinations of other variables – like type of radicals, vapor pressure or polarity of the compounds – have also been suggested as indicators.

According to our present knowledge, the response of the nerves may be described 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 concentrations of chemicals in the air, the concentration of absorbed molecules in mucosa and the number of activated receptors.

A simplified chemical and physical model, therefore, includes three steps which describe the absorption of airborne pollutants into the liquids of the mucosal membrane, and the subsequent binding to the receptor, which is followed by reactivation of the receptor. Such a model has previously been described in the literature (Nielsen et al., 1985b; Nielsen et al., 1988; Kristiansen et al., 1988) and among other things assumes ideal gas conditions of the air phase and a lipophilic receptor compartment. In Mølhave et al. (1992) this model has been used to identify the short-cuts made in the derivation of the TVOC indicator. It appears that the TVOC indicator under specified assumptions is an estimation of the lower level of perceived unspecific stimulation of nerves in a population after exposure to VOC's. The response may be proportional to the sum of mass-concentrations (mg/m^3) of the compounds in the air if the following assumptions are made:

- The response is caused by unspecific stimulation of lipophilic sensors which respond additively to a multicomponent exposure.
- The compounds can be assumed to react equally strongly with the unspecific sensors, i.e., the equilibrium constants of the compounds can be assumed to be within limited ranges.
- The molecular weights and the vapor-pressures of the compounds are assumed to be within limited ranges.
- The exposures do not include compounds that react chemically with the receptor, e.g. formaldehyde or acrolein. Such reactions may cause an additional reaction to be added to the estimated lower limit for unspecific response.
- The indicator cannot be used to predict other types of effect, for example effects on CNS, tissue changes or cancer.

The simplifications used in Mølhave et al. (1992) to develop this TVOC concept are based on experimental evidence. However, it must be emphasized that the TVOC concept has not yet been thoroughly tested in practice and therefore is still a postulate.

Some Investigations and Controlled Experiments with Low-level VOC Exposure and Health Effects

Field Investigations

The dominating effects or symptoms caused by low-level exposures to VOC's are similar to those associated with the sick building syndrome as defined by WHO (WHO, 1982). These acute or subacute effects appear among a major part of the occupants in buildings. Generally, no excessive environmental exposure can be identified and the occupants seem to be without any unusual sensitivity.

The WHO group (WHO, 1982) stated that more than 30% of all new buildings seem to be affected by these indoor climate problems which further seem to have no evident cause. The symptoms included in the syndrome may be observed in any group of persons and the "sick buildings" are characterized by a large fraction of the occupants having the symptoms. The syndrome, therefore, seems to be a normal reaction of the normal population to unfavorable indoor climates.

No investigation of this postulated SBS syndrome has been reported in which a complete and well-defined spectrum of symptoms was used. Generally, the descriptions of the symptoms in the literature are anecdotal and unsystematic. Criteria for causality such as those shown in Tables 3 and 4 are not yet fulfilled and, therefore, SBS still appears to be a postulate.

A review of investigations dealing with low-level exposures to VOC's and their influence on health should preferably deal with both acute and subacute effects. In most investigations this distinction is reflected in a distinction between job- and building-related effects or symptoms. Such a time selectivity is inadequate in relation to most sensory effects, which may show strong intensity variations within seconds or minutes. In the investigations, the symptoms further should show a correlation to VOC exposures. Due to the many VOC's normally found in indoor environments, the results of concentration measurements in practice are often impossible to interpret as measures of exposure for occupants. Such measurements, further, are expensive. Only a few investigations, therefore, report adequate information on VOC-exposure levels. In some reports, indications of possible VOC influence on indoor air quality may be deduced if the type or intensity of ventilation is correlated to the prevalence of symptoms. Such indications, however, are not used in this summary as causalities other than VOC's may be active in these cases (e.g. humidifier fever).

In a previously reported summary of indoor air investigations (Johansson, 1982) eight of the 12 investigations described human reactions. These eight and a few more investigations were summarized in a previous publication (Mølhave, 1986). The average VOC concentrations in houses with indoor climate problems were 1.3 mg/m^3 with a range from 0.09 to 13 mg/m^3, while the concentration in houses where no problems were reported showed an average of 0.36 mg/m^3 ranging from 0.02 to 1.7 mg/m^3. Complaints seem to appear in all field investigations reporting concentrations exceeding 1.7 mg/m^3.

The "no-effect level" could not be estimated from these field investigations. In a more recent investigation (The Danish "Town Hall" study (Zweers et al., 1990)) a significant correlation was found between both TVOC and olf or decipol exposure indicators in the rooms and mucosal irritation or work-related symptoms. The threshold for effects of VOC's on air quality was estimated to be between 0.19 mg/m^3 and 0.66 mg/m^3 (TVOC). The lower threshold for effects, therefore, may be as low as 0.2 mg/m^3 depending on other simultaneous exposures.

Controlled Experiments with Low-level VOC Exposure and Health Effects

Investigations and experiments with controlled low levels of volatile organic compounds (VOC's) are, for several reasons, more difficult to interpret than traditional clinical investigations and experiments with toxic compounds (Mølhave, 1991b). At present, few acceptable objective measures exist for effects. These low-level experiments often use unspecific subjective reactions as the only available measures of effects. This has a number of consequences for the experiments. These limitations reduce their usefulness for conclusions about causality at low exposure level.

- Group or population responses are often used instead of the objective measures of effects.
- More co-factors must be controlled than in traditional experiments both in relation to exposure conditions, to the subjects and to their sensitivity. Exposure duration, time of day, self-reported sensitivity, and occupation seem to be important co-variables.
- A spectrum of several symptoms or signs must be included in the tests due to the unspecific nature of the effects.
- The number of possible interactions at low-level exposure is so large that at present there seems little chance of investigating their etiology in detail.
- Intersubject variation is so large that the subjects are used as their own controls. Repeated measurements may, however, lead to effects from learning or from different times of the day, week or year. Proper baseline measurements, therefore, are difficult to arrange.
- New undocumented methods or old methods outside their documented range are often used and often without proper quality assurance programs.

- Double-blind designs are impossible to arrange because of the perceived exposure. Special considerations are needed in low-level experiments to establish causality.
- Registration of motivation and attitudes are especially important for experiments using registration of perceived exposure and symptoms as measures of effects.

Experiments at higher exposure level, e.g. experiments around or above occupational threshold limit values, often focus on health effects that are much more severe for the affected few persons than the relatively harmless, but more frequently appearing, comfort-reduction caused, e.g., by mucous membrane irritation. Also, these high-level exposure experiments may use only a healthy adult population, excluding more sensitive groups such as children or older persons. Further, the high-level exposure experiments may include exposure times different from normal non-industrial occupancy.

Few occupational experiments, therefore, are relevant for extrapolation to the low range of concentrations found in non-industrial indoor environments. Some experiments have been performed in which humans have been exposed to low levels of VOC. Four controlled exposure experiments were established in the climate chamber at our institute to test if low exposure levels of VOC's may cause reduced well-being or discomfort (Mølhave et al., 1986; Mølhave et al., 1991; Kjærgaard et al., 1989; Kjærgaard et al., 1991). A more recent experiment in the USA replicated the first of these Danish experiments (Otto et al., 1990). These experiments are summarized in Tables 6 and 7.

In the first Danish experiment, humans were exposed to small concentrations of a mixture of 22 normally occurring air pollutants (Mølhave et al., 1986). These compounds are all known to be emitted from building materials. It follows from the experiment that air quality may be significant-

Table 7 Summary of 5 exposure experiments.

Ref.	Exposure		Population		Measures of effects
	type	mg/m^3	type	number	
1	M22	0, 5, 25	Randomly selected but SBS-sensitive	64	Subjective sensory responses, indications of neurologic effects and changes in eye and nose liquids
2	M22	0, 1, 3, 8, 25	Randomly selected and healthy	25	Sensory symptoms, headache and general well-being
3	n-decane	0, 40, 140, 400	Random, healthy	63	Sensory symptoms. Tear film stability. Leukocytes in eye liquids
4	M22	0, 25	Healthy SBS subjects	21 14	Sensory symptoms Lung function Leukocytes in eye liquids and nasal secretions. Performance
5	M22	0, 25	Healthy males	76	Sensory symptoms Neurobehavioral tests

M22 = standard mixture of 22 indoor air pollutants.

1 Mølhave et al., 1986.
2 Mølhave et al., 1990a.
3 Kjærgaard et al., 1989.
4 Kjærgaard et al., 1991.
5 Otto et al., 1990.

ly reduced at TVOC concentrations of 25 mg/m^3 and that odor appears at 5 mg/m^3. The effects are acute and occur within minutes after the start of exposure and no statistically significant adaptation is seen except for odor intensity (Mølhave et al., 1986). These findings have been confirmed in all subsequent experiments.

In the first Danish exposure experiment, some indications were found of objective effects related to odor threshold, to chemical changes in eye and nose liquids, and to performance and mood (Mølhave et al., 1986). Irritation of eye and nose, therefore, may not be the only effect to consider as a result of exposure to VOC's.

The major aim of the second Danish exposure experiment was to measure dose-response relationships between human sensory reactions and exposure to the same mixture of VOC's as used in the first experiment. This second experiment focused on the dose-response relationships of sensory irritative symptoms and headache (Mølhave et al., 1991a). Further, the importance of these two symptoms for the feeling of general well-being was examined.

In the experiment, the subjective reactions indicate that a statistically significant odor was registered at 3 mg/m^3. This indicates that the lower limit for complaints resulting from this type of air pollution in general living spaces is at or below 3 mg/m^3.

The air quality was rated unpleasant only at concentrations at or above 8 mg/m^3 where the need for additional ventilation or removal of sources became evident. Also, the irritation of the mucous membranes was statistically significant only at concentrations at or higher than 8 mg/m^3 for 50-min exposures. In the first study, no statistically significant irritation was found at 5 mg/m^3 after 2.75 hours' exposure (Mølhave et al., 1986).

In the experiment the same general trend was found at concentrations lower than the lowest exposures causing statistically significant effects. The effects, therefore, would probably have been significant at lower exposure levels if more subjects had been examined, if a longer exposure time had been used, or if other indoor climate factors had been slightly uncomfortable.

The third of the Danish experiments was a dose-response study of human reactions to the indoor air pollutant n-decane (Kjærgaard et al., 1989). 63 healthy subjects, randomly selected from the normal population, were exposed to n-decane concentrations of either 0, 10, 35 or 100 µl/l. Of these exposures, only 10 µl/l (or about 40 mg/m^3) is relevant for new buildings. The statistically most significant findings were dose-dependent changes in perceived irritation of mucous membranes, increased sensation of odor intensity and reduced air quality. Adaptation was seen at the highest exposure levels, but not at the levels relevant for a non-industrial environment. The physiological measurements showed decreased tear film stability at all exposure concentrations (Kjærgaard et al., 1989).

The number of leukocytes in eye liquids increased in a dose-related manner. Predictors of the sensitivity to exposure, e.g. threshold for mucous membrane irritation and skin irritation (Stinging skin test), were correlated to subjective ratings of odor intensity and irritation of mucous membranes (Kjærgaard et al., 1989).

The fourth Danish experiment was a controlled experimental study of human reactions to 25 mg/m^3 of the mixture of the 22 volatile organic compounds used in previous experiments (Kjærgaard et al., 1991). 21 healthy subjects were compared with a group of 14 subjects suffering from the sick building syndrome (SBS subjects), i.e. having symptoms such as irritated mucous membranes and headache related to buildings. Both groups reacted subjectively to the indoor air pollutants and reported worse odor in a questionnaire, worse indoor air quality and more irritated mucous membranes in eye, throat and nose than in the clean environment.

A tendency to a stronger response was seen among the SBS subjects. Objective measures indicated exposure-related reduction of lung function among the SBS subjects. Both groups had an increased number of polymorphonuclear leukocytes in tear fluid as a result of exposure. This was not seen in nasal secretions. Psychological performance was diminished by exposure (Kjærgaard et al., 1991).

The American experiment (Otto et al., 1989) is the most recent and was aimed at confirming and extending the first Danish experiment. Only two neurobehavioral performance tests were used in the Danish study, while 14 tests were used in the American study to fully characterize the possible neurobehavioral effects of VOC exposure on young healthy white males.

Results of the study confirm the adverse subjective reactions of subjects to a 25 mg/m^3 concentration of volatile organic compounds. Ratings of general discomfort (defined as irritation of the eyes, nose and throat), symptom questionnaire responses on odor intensity, air quality, eye and throat irritation, headache and drowsiness, and mood scale measures of fatigue and confusion all differed in predicted directions between clean air and exposure conditions. No convincing evidence was found of any neurobehavioral impairment associated with exposure to the VOC mixture.

However, it could not be concluded that a 25 mg/m^3 concentration of VOC's poses no neurotoxic risk to susceptible subgroups or even to the general population. In summary, clear adverse subjective reactions to VOC exposure, but no functional (neurobehavioral) impairment, were found (Otto et al., 1989).

The American experiment further confirmed that subjective reactions to VOC's at levels found in new buildings are not limited to "complainers" or chemically sensitive subgroups in the general population.

Discussion

Henle-Kock Criteria

In order to be accepted, any proposed causality between VOC and health must fulfill criteria such as the Henle-Kock criteria shown in Tables 3 and 4. It must be emphasized that, although fulfillment of these criteria is strong evidence for a proposed causality, this may not be a sufficient or a final proof.

Are the Criteria for an Acceptable Causality between VOC Exposure and Health Fulfilled?

Table 6 summarizes the conclusions of the five previously mentioned experiments dealing with low-level VOC exposures. The Table shows the positive or negative findings at different TVOC levels in relation to the main types of effects expected according to the suggested biological model (Mølhave, 1990b).

The experiments indicate that, in controlled exposures, effects follow exposure to VOC's as required according to criterion 3 in the Henle-Kock criteria shown in Table 3. Perceptive effects are observed at TVOC concentrations higher than 3 mg/m^3. Other subjective effects follow higher exposures.

Few inflammatory reactions were reported although some of the irritative effects may be of inflammatory origin or may be caused by chemical mediators. Changed tearfilm stability and cell counts were seen at 25 mg/m^3. Subjects also reported changed temperature sensation in the exposed skin areas at 25 mg/m^3. These observations may indicate weak inflammatory reactions.

A 25 mg/m^3 level seems to cause weak environmental stress symptoms like headache and drowsiness. Associated psychological effects such as changed performance, confusion and fatigue are also found at 25 mg/m^3. These effects are known from higher exposure levels, but have not been consistently found in low-level exposure experiments. At present, 25 mg/m^3 seem to be the lowest controlled exposure which has indicated such psychological effects.

These experimental findings show that measurable group responses are found in controlled exposure experiments as required in criterion 2. The responses follow a gradient from sensory effects (odor 3 mg/m^3) and indications of subacute inflammatory reactions (changed leukocytes in liquids, perceived skin temperature at 25 mg/m^3) and indications of subacute stress-reactions at 25 mg/m^3. The criterion 1 of progression of the effects, therefore, also seems fulfilled.

The total environmental exposure in most field investigations is multifactorial as factors other than VOC exposure may exceed their no-effect levels. Most of the effects reported in field investigations, therefore, may have more than one cause. Consequently, it is not surprising that effects of VOC exposures in field investigations seem to occur at lower exposure levels than in controlled experiments where exposure factors other than VOC's are supposed to be below their no-effect levels. Further, in the clinical experiments the exposure times were less than 3 hours which, from field experience, seems too short a period to cause severe subacute effects at low exposure levels. Much more research is needed to finally establish whether subacute effects may occur after prolonged exposures.

In a review of field investigations, it was found that complaints seem to arise when the concentrations exceed 1.7 mg/m^3. Below 1.7 mg/m^3, complaints may arise if other types of simultaneous exposures are present (Mølhave, 1986). The concentrations reported from field investigations are improperly documented and they may be biased. The published investigations do, however, indicate that the concentrations of volatile organic compounds are generally higher in problem houses than in the houses without problems (Mølhave, 1986).

A recent field investigation finds an effect of VOC's at concentrations in the range from 0.05 to 1.38 mg/m^3 (Nordbäck, 1990). The exposure range from 0.19 mg/m^3 to 0.66 mg/m^3 was estimated in the Danish Town Hall Study for the lower threshold of no-effects (Zweers et al., 1990). This range corresponds to the range of the lower limit of concentrations in buildings with complaints and is at present the best estimate of the lower exposure limit for no-effects of VOC's.

Reactions do not seem to be related to a hypersensitive group of subjects. The same reactions were found among normal healthy subjects in the Danish experiments (Mølhave et al., 1986, 1991; Kjærgaard et al., 1989, 1991) and in the American experiment (Otto et al., 1989). Subjects responding most strongly did, however, seem to have special characteristics such as stronger skin-response to irritating compounds (Kjærgaard et al., 1991) and, among persons claiming often to suffer from Sick Building Syndrome, a significant, but only slightly stronger response was found (Kjærgaard et al., 1991). These SBS subjects also showed indications of lung-functional changes (Kjærgaard et al., 1991). However, the five controlled experiments contain few or no consistent investigations of lung function, allergic or systemic effects.

No definitive conclusion can be drawn with respect to the influence of other co-factors. In those few investigations dealing with such factors, both positive and negative indications were found. The information, however, indicates that future research with more sensitive experimental designs and analytical methods may show such effects.

In the published field investigations, the observed symptoms are not systematically described. However, they appear to be more frequent among exposed than among non-exposed persons. The field investigations, therefore, also indicate that criterion 3 may be fulfilled. Future research, however, will have to prove this.

The laboratory experiments indicate that the effects which are expected according to the biological model can be experimentally reproduced and acutely follow the exposure. The criteria 4 and 6, therefore, are also fulfilled. No field investigations have been reported of tests of the effects of elimination or modifications of VOC exposure. Post-exposure measurements during the controlled experiments, however, indicate that the effects are reversible and disappear shortly after exposure. The 5th criterion, therefore, may also be fulfilled.

In conclusion, no evidence contradicts the proposed causality between the effects tentatively related to low-level exposure to VOC's. On the contrary, evidence from both field investigations and controlled exposure experiments does support the causality. The field investigations and controlled experiments are, however, as yet too few to allow a final conclusion to be drawn.

Does an Acceptable Biological Model exist for the Reactions to Low-level Exposures to VOC?

In Table 4 a set of four criteria was established which any acceptable biological model for the causality of a proposed etiology must fulfill. The first criterion was that the model must explain the observed effects. The list of effects expected – according to the model in Figure 1 – to follow from low-level exposure to VOC's coincides very well with the effects observed in epidemiological field investigations and controlled experiments. It appears that sensory irritation, olfaction, irritation, and weak neurological effects seem to be the dominating effects of low-level VOC exposure. The first criterion for an acceptable model, therefore, seems to be fulfilled.

The effects are all known from similar or higher exposure levels. The third criterion, therefore, is fulfilled. Any delay in effects caused by low-level exposure has yet to be identified. Some indications of a sub-acute latency exist. According to the model, such a latency of the effects is explained by the subacute skin and stress reactions following prolonged exposures. Therefore, the fourth criterion also seems to be fulfilled.

The model does not include acceptable measures of a combined exposure to the many compounds simultaneously found indoors. Some indicator measures have been suggested. These indicator measures are all based on simplifications of which only some have been justified and fewer thoroughly investigated. At present, they 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 few acceptable measures or indicators exist for possible co-variables related to the model. Criterion 2 dealing with acceptable measures or indicators of an exposure, therefore, is not yet fulfilled.

Tentative Guidelines for VOC's in Non-industrial Environments

The observations summarized here have major limitations. They do, however, indicate that VOC's may be important for indoor air quality, especially in the form of discomfort due to odors and irritative symptoms in eyes, nose, and throat, and headache. The list may include other effects, for example related to productivity and performance. Such effects have not yet been positively identified.

The tentative conclusion from the available epidemiological studies (Mølhave, 1986; Mølhave, 1990a) and the exposure experiments is summarized in Table 8. It indicates that no effects are expected as a result of exposure to VOC's below about 0.2 mg/m^3.

At concentrations higher than about 3 mg/m^3, complaints seem to occur in all investigated buildings with occupants having symptoms. In controlled exposure experiments, odors are significant at 3 mg/m^3.

At 5 mg/m^3, objective effects were indicated besides the subjective irritation. Exposures for 50 minutes to 8 mg/m^3 led to significant irritation of mucous membranes in eyes, nose and throat.

In the reviewed literature, few acceptable indications of exposure levels are given

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which allow an estimate of the threshold for headache. Concentrations below 3 mg/m³ in field investigations were found to show a significant difference in frequencies of headache between problem buildings and control buildings. On the other hand, significant headache was found in only one of the exposure experiments and then at 25 mg/m³.

The reason for the lower threshold in field investigations may be either the interaction of other exposures, or the effect of longer exposure durations. Therefore, based on the present information, the threshold for headache and other weak neurotoxic effects caused by exposure of less than a few hours' duration is expected to be between 3 and 25 mg/m³.

These conclusions refer to the more prevalent of the effects caused by VOC exposure among normal subjects. Risk groups may exist that respond more than the normal population. Indications of lung function reactions were found in a pilot study on allergic persons exposed to 25 mg/m³ VOC (Harving et al., 1989). Further, future investigations dealing with larger groups of persons may reveal special effects such as allergy or carcinogenicity from low-level exposures to VOC's. These special effects, however, have not been demonstrated to follow from exposure to the type of compounds and concentrations of VOC's found in indoor air.

Consequences of the Proposed Model for Building Construction

A sense of well-being is an essential part of general health. This is not always reflected in discussions of indoor air quality, which are often focused only on absence of objectively defined diseases. One reason for this one-sided discussion is that annoyance and IAQ have not yet been defined and at present cannot be objectively measured. Further, no relevant measures exist of combined multifactorial exposures. However, the unacceptably high prevalence in buildings of complaints about reduced comfort or well-being and the associated indirect effects on productivity, etc., will continue if development of objective measurements of exposures and effects are neglected and discomfort continues to be considered irrelevant to health effects in the evaluation of indoor air quality.

Table 8 Tentative dose-response relationship for discomfort resulting from exposure to solvent-like volatile organic compounds as air pollutants in non-industrial indoor environments.

Total concentration[a] mg/m³	Irritation and discomfort	Exposure range
< 0.20	No irritation or discomfort	The comfort range
0.20-3.0	Irritation and discomfort possible if other exposures interact	The range of multifactorial exposures
3.0-25	Exposure effect and probable headache possible if other exposures interact	The range of discomfort
> 25[b]	Headache. Additional neurotoxic effects other than headache may occur	The toxic exposure range

[a] Measured as TVOC according to Mølhave et al. (1992).
[b] This range is only partly discussed in this paper.

An important consequence of the lack of objective measures of exposure and effect in relation to low-level exposures to VOC's is that dose-response relationships have not yet been established for discomfort. A dose-response relationship is the relation between exposure (concentration and duration) and effect and may be used for risk assessment and regulation, etc. For most diseases or adverse health effects such relations exist. Toxicological risk assessment, therefore, has been developed and is operational for mitigation of these diseases. Quantitative evaluations of the risks of adverse irreversible health effects (e.g. related to CO or Radon) or to the risks of reversible or irreversible changes of the body's physiological functions (e.g. CNS or PNS effects) are used in traditional occupational or environmental evaluation of health risks related to airborne agents. These assessments are made according to standard toxicological principles and the results are, e.g., TLV's for air pollutants, occupational standards for light levels (LUX), and sound levels (dB(A)).

The comfort dimension of health refers to qualitative evaluations of the environment and, in many respects, it is a new concept for regulation. The air-deodorants, paints, wallpapers or music that are liked by some persons are disliked by others and generally accepted principles for regulation of the quality of the indoor environment with respect to odors, sounds, colors etc, may seem impossible to establish, if desired at all. Some general conclusions for the principles for optimizing of the indoor climate, however, may be drawn if references are made to regulations, e.g., in building codes for the acoustic or the lighting environment which contain additional qualitative concerns besides those used for the setting of the TLV type of guidelines.

The first basic principle implicit for these guidelines is that the building must support a specified range of human activities, habits and preferences. Complaints and decreased performance will automatically follow if the occupants try to perform activities outside this range, e.g. reading in too dark a room with disturbing intermittent noise peaks, or working with a video screen with many light reflections. This range of activity may be different for homes and offices etc., as the activity patterns in homes include recreation, rest and sleep, and other activities not normally found in offices. Further, the occupants of homes may be more sensitive than the working population as they include the sick, young and old fraction of the population.

The second basic principle originates from the assumption that humans do not feel well if they are deprived of the optimal use of their senses to perceive their environment and the activities they are performing. The ideal indoor environment, therefore, seems to allow the occupants to use their senses to pick up wanted environmental signals undisturbed by exposures carrying unwanted signals or information. This means that unwanted environmental information, like the sound of typing from a colleague in the same room, or the neighbor's radio in a home, should be muffled. On the other hand, conversation among the occupants or their perception of their own activities should be eased. In short, this second principle calls for an optimization of the signal-to-noise ratio for the senses by allowing the wanted signals to propagate to the occupants and the unwanted sensory signals to be dampened.

This second principle, if true, explains why different occupants have different optimal environments. The signals which bear information to one person about his or her own activity and environment create sensory "noise" for another person. Therefore, the signals relevant for one person differ from those relevant for another.

In the special case of VOC pollutants and occupants' comfort, the relevant senses are the combined set of senses, including olfaction and the common chemical sense. A way of explaining occupant responses to VOC's, therefore, could be that the combined sensory signals resulting from chemical exposures inform the occupants about the presence of dangerous or beneficial sources of volatile organic compounds. These senses are probably very old in terms of evolution and they help us to avoid dangers such as fires or wild animals, to find edible food, and to identify other humans. In offices, as in homes, the sensory signals indicate the presence of sources such as special activities, processes or utensils. This may be meaningful information to the occupants and, as such, desired information.

Not all VOC's bring positive information to each individual. An office worker may not feel relaxed and comfortable if he or she constantly feel a weak eye or nose irritation indicating the presence of an unknown health risk. Such a risk may be caused, e.g., by an unidentified chemical exposure brought to the occupants through the ventilation system from unknown sources somewhere in the building. The office worker, of course, will try to remove any suspected source, open windows, etc., in order to mitigate the unidentified "enemy" and thus be constantly alert.

The present practice of setting standards or guidelines for perceived air quality (PIAQ) takes the form of concentrations which are expected to result in a certain proportion of a population detecting or recognizing the exposure (WHO, 1989). To the extent that these guidelines do not distinguish between wanted and unwanted exposures, they contradict the principle of signal-to-noise optimization.

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