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Development of New VOC Exposure Metrics and Their Relationship to "Sick Building Syndrome" Symptoms

J. Ten Brinke
(Ph.D. Thesis)

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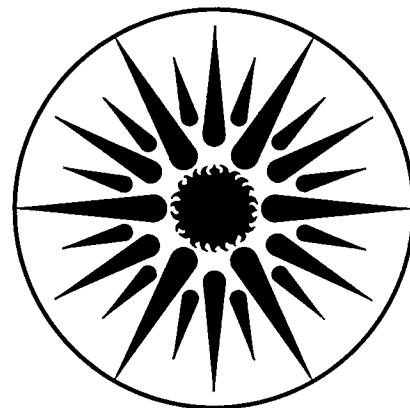
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Ph.D. Thesis

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by

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JoAnn Ten Brinke

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Committee in charge:

Dr. Joan M. Daisey, Co-Chair
Professor Catherine P. Koshland, Co-Chair
Professor Steve Selvin
Professor Gene Rochlin

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Abstract

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JoAnn Ten Brinke

Doctor of Public Health

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. Dr. Joan M. Daisey, Co-Chair

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Volatile organic compounds (VOCs) are suspected to contribute significantly to "Sick Building Syndrome" (SBS), a complex of subchronic symptoms that occurs during and in general decreases away from occupancy of the building in question. Prior attempts to link exposures to VOCs and symptom outcomes have not considered potencies; i.e., the level of response for a given dose, of these compounds. A new approach takes into account individual VOC potencies, as well as the highly correlated nature of the complex VOC mixtures found indoors. The new VOC metrics are statistically significant predictors of symptom outcomes from the California Healthy Buildings Study data. Multivariate logistic regression analyses were used to test the hypothesis that a summary measure of the VOC mixture, other risk factors, and covariates for each worker will lead to better prediction of symptom outcome. VOC metrics based on animal irritancy measures and principal component analysis had the most influence in the prediction of eye, dermal, and nasal

symptoms. After adjustment, a water-based paints and solvents source was found to be associated with dermal (OR=2.2, 95% CI 1.3-3.7) and eye (OR=1.7, 95% CI 1.1-2.7) irritation. The more typical VOC exposure metrics used in prior analyses were not useful in symptom prediction in the adjusted model (total VOC (TVOC), or sum of individually identified VOCs (ΣVOC_i)). Also not useful were three other VOC metrics that took into account potency, but did not adjust for the highly correlated nature of the data set, or the presence of VOCs that were not measured. High TVOC values (2-7 mg m^{-3}) due to the presence of liquid-process photocopiers observed in several study spaces significantly influenced symptoms. Analyses without the high TVOC values reduced, but did not eliminate the ability of the VOC exposure metric based on irritancy and principal component analysis to explain symptom outcome.

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Acknowledgments

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Introduction

Background

There has been considerable focus on the air quality of industrial settings

due to the elevated levels of pollutants and their significant adverse health

effects for industrial workers. However, in recent decades problems in

office buildings have been reported with increasing occurrence. These

problems include "sick building syndrome" (SBS) and building related

illness (BRI). As defined by the United States Environmental Protection

Agency (1988), BRI refers to occupant exposure to indoor contaminants

that results in a clinically defined illness characterized by symptoms of

cough, fever, chills, and muscle aches. With BRI there is typically evidence

of exposures to some agent at or near a level known to cause the health

effect in question. Examples of BRI include Legionnaires disease and

carbon monoxide poisoning due to motor vehicle emissions drawn into the building (e.g., when a loading dock is located near air intake). BRI complainants may require long recovery times after leaving the building. While BRI occurs where causal factors have been identified, SBS occurs where no environmental parameters are near a health threshold. A building is considered to manifest SBS when a large percentage of occupants report a specific suite of symptoms (discussed below), the cause of symptoms is not known but indoor air quality is suspected to play a role, and the occupants report that the symptoms decrease when they leave from the building in question.

"Sick building syndrome" (SBS), defined by the World Health Organization (1983), is comprised of a complex of subchronic symptoms that occur during and generally decrease away from occupancy of the building in question. The symptoms include:

- eye, nose and throat irritation;
- sensation of dry mucous membranes and skin;
- erythema;
- mental fatigue;
- headaches and elevated frequency of airway infections an cough;
- hoarseness, wheezing, and unspecific hypersensitivity; and
- nausea, dizziness.

The frequency of these type of nonspecific complaints can be high in any population; however, by 1983 the increasing number of cases with similar symptoms prompted the World Health Organization (WHO) to report "it is reasonable to assume that we are dealing with a true environmental problem (World Health Organization, 1983)." Extreme cases of sick building syndrome have been reported where buildings were found to be uninhabitable, individuals were evacuated and the building abandoned. Some buildings

are temporarily "sick," where the symptoms appear to decrease after approximately half a year. These temporarily sick buildings tend to be either newly constructed or newly remodeled buildings. Other buildings appear to be permanently "sick." Symptoms persist in spite of various remedial actions.

From 1971 through December 1984, the National Institute of Occupational Safety and Health (NIOSH) conducted 446 health hazard investigations in public access buildings where health complaints had been reported[1], and determined the primary environmental deficiency. An overview of the results of these studies are reported by Gorman and Wallingford (1989). The investigations were in response to existing worker health complaints and illness, and are not therefore representative of a statistically valid cross-section of indoor air quality problems. The buildings included government and private sector office buildings, schools, colleges, and health care facilities. In 88% of the cases the buildings were temporarily sick. Primary problems were identified as due to building material contaminants (3%), microbiological contaminants (5%), contaminants brought in from outside the building (11%), contaminants from inside the building (19%), inadequate ventilation problems (52%). The remaining 12% of the buildings were permanently sick buildings, where no specific problem could be identified. The overview probably underestimates the percentage of buildings in which causes could not be completely identified. As per Mendell (1995), although the report lists the *primary* environmental deficiency determined, NIOSH has since recognized that most problem buildings have

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1. Excluding buildings with asbestos, a different type of problem

"multiple environmental deficiencies," and that there are difficulties in determining specific causes of health complaints:

> "... in 104 recent (1993) investigations performed by NIOSH, with standardized collection of information, and multiple problems potentially identified in each building, 101 of the 104 had multiple problems identified (i.e., a single problem alone was identified in only 3 buildings) ...." (Crandall and Kieber, 1995)

Persistently "sick" buildings have several common features. These include (World Health Organization, 1983):

- building-wide forced ventilation system, that recirculates air with various percentages of outdoor air make-up, sometimes including inappropriate locations of air intake value (near sources of pollutants, for example, located in the basement garage);
- buildings of relatively light construction;
- buildings of energy-efficient design, with a centrally-controlled, homogeneous thermal environment, often kept relatively warm;
- airtight building envelopes (windows permanently sealed).

To date, the etiology of "sick building syndrome" is not completely understood and certainly no specific causative factor has been identified; however, an emerging body of data indicate that SBS symptoms are widely prevalent and that there is more of a continuum than previously expected. Overall prevalence of symptoms in buildings *without known problems* is reported at greater than 20% (World Health Organization, 1983; Hedge et al., 1989; Norback and Torgen, 1990; Mendell, 1991; Zweers et al., 1992; Fisk et al., 1993). The syndrome is hypothesized to be of a multifactorial origin as no single environmental parameter in the buildings is near a health threshold.

Investigations of SBS have been hampered by problems inherent to this type of research. It is difficult to develop objective information on cause and effect in buildings that have

had cases of SBS problems because the 'system has been perturbed'. Buildings known for worker complaints are often termed "problem" or "complaint" buildings. Knowledge of building complaint status can bias symptom reporting upwards, an effect referred to as "reporting bias." Additionally, outcome measures, i.e. symptoms, are themselves subjective measurements.

Current Hypotheses on the Etiology of "Sick Building Syndrome"

Current hypotheses on the cause of SBS incorporate consideration of various chemical, physical, biological and psychosocial elements. In the literature on SBS, these elements are in turn grouped into general categories: job and personal factors, building factors, workspace factors, and environmental factors. A recent review article summarizes the hypotheses on the etiology of SBS found in the epidemiologic literature. Mendell (1993) reviewed the findings of 32 studies of 37 factors hypothesized to be related to non-specific symptoms reported by office workers. Excluded for brevity were all reports of single complaint building investigations, some reports of smaller studies, and studies performed in laboratories. Articles included in the review were those from 1984 through December 1992. Table 1 summarizes reported factors[1] which have been hypothesized to contribute to SBS, and which have been evaluated to some extent in field studies.

Findings across the studies were defined as "consistent" where there was "agreement by all relevant studies reviewed, with a minimum of three studies" (Mendell, 1993). Overall

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1. Some of the factors listed in Table 1 are indirect, e.g., some agent associated with the air conditioning system rather than the air conditioning system per se is believed to be the direct causative factor.

TABLE 1. Factors and environmental variables hypothesized to contribute to SBS [a]

Job & Personal	Building	Workspace	Environmental
• allergies ++ • asthma ++ • clerical job ? • carbonless copy use ? • female gender + • job stress/dissatisfaction ++ • photocopier use ? • smoker ? • VDT use +	• air-conditioning ++ • humidification ? • low ventilation rate + • mechanical ventilation (no a.c.) ? • newer building ? • poor ventilation maintenance ?	• carpets + • improved office cleaning ? • environmental tobacco smoke ? • fleecy materials/ open shelves ? • ionization ? • photocopier in room or near ? • more workers in space +	• air velocity o • total viable bacteria o • beta-1,3-glucan ? • carbon monoxide o • endotoxins ? • floor dust (all or protein) ? • formaldehyde o • total viable fungi o • low humidity ? • low negative ions ? • light intensity or glare ? • noise o • respirable particles ? • total particles o • high temperature ? • total VOCs ?

a. Modified from (Mendell, 1993).
++ - Consistent higher symptoms.
+ - Mostly consistent higher symptoms.
o - Consistent lack of association.
o - Mostly consistent lack of association.
? - Sparse or inconsistent findings.

findings from the literature review are that symptoms are *positively* associated with low

ventilation rates (at or below 10 liters/second/person) (Jaakkola et al., 1991; Sundell et al.,

1994), air-conditioning (Hedge et al., 1989; Skov et al., 1990; Mendell, 1991; Zweers et

al., 1992), carpets (Norback and Torgen, 1989; Norback and Torgen, 1990; Skov et al.,

1990; Mendell, 1991), more workers in a space (Skov et al., 1989; Skov et al., 1990;

Hodgson et al., 1991; Mendell, 1991; Zweers et al., 1992), VDT use (Hedge et al., 1989;

Skov et al., 1989; Zweers et al., 1992), female gender (Hedge et al., 1989; Skov et al.,

1989; Burge et al., 1990; Skov et al., 1990; Jaakkola et al., 1991; Mendell, 1991; Zweers et al., 1992), job stress/dissatisfaction (Hedge et al., 1989; Norback and Torgen, 1990; Jaakkola et al., 1991; Mendell, 1991; Zweers et al., 1992), allergies/asthma (Skov et al., 1989; Jaakkola et al., 1991; Mendell, 1991; Zweers et al., 1992). Consistent or mostly consistent findings of *no* association with symptoms were reported for total viable fungi (Skov et al., 1990; Skov et al., 1990; Mendell, 1991), total viable bacteria (Skov et al., 1990; Skov et al., 1990; Mendell, 1991), total particles (Skov et al., 1990; Skov et al., 1990), air velocity (Burge et al., 1990; Skov et al., 1990; Hodgson et al., 1991), carbon monoxide (Hodgson et al., 1991; Mendell, 1991), formaldehyde (Skov et al., 1990) and noise (Burge et al., 1990; Skov et al., 1990; Hodgson et al., 1991; Zweers et al., 1992).

Findings for remaining factors, over half (59%), found to be "sparse or inconsistent findings," indicate either 1) few studies had considered the factor, but the results showed strong association between factor and symptom, or, 2) multiple studies found positive, negative or no associations with symptoms. These included: total volatile organic compounds (TVOCs), respirable particles, floor dust (all or protein), endotoxins, β-1,3-glucans, low negative ions, high temperature, low humidity, light intensity or glare, mechanical ventilation, newer building, poor ventilation maintenance, ionization, improved office cleaning, fleecy materials/open shelves, photocopier in room or near, environmental tobacco smoke, clerical job, carbonless copy use, photocopier use, smoker.

An example of the first type of inconsistency is the job and personal factor photocopier use. Two studies showed positive association (Skov et al., 1989; Mendell, 1991), but

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photocopier use is classified as inconsistent due to the limited number of studies (three studies defined the minimum for consistency). The workspace factor of proximity of photocopier workspace is an example of the second type of inconsistency, with no association (Mendell, 1991) and positive association (Sundell et al., 1994) with symptoms. It should be noted that having identified photocopier use as a probably SBS factor, the cause and effect relationship still remains unknown. That is, it is not clear if chemicals emitted into the air are inhaled, or if dermal exposure to less volatile chemicals cause any or all of the SBS symptoms, or if some other agent is involved.

The environmental measurement total volatile organic compound (TVOC) is a further example of the second type of inconsistency, with various studies reporting different findings. Six observational studies considered the relationship between TVOC exposure and symptom prevalence. TVOC concentrations were found to be positively associated with symptoms in three studies (Norback and Torgen, 1990; Hodgson et al., 1991; Hodgson et al., 1992), but were found to have no associations in three separate studies (Skov et al., 1990; Skov et al., 1990; Mendell, 1991).

Hypotheses comprised of the factors discussed above have not withstood the rigorous testing necessary to resolve the cause of SBS. Although these various elements may ultimately represent multifactorial determinants, at this point in our understanding they remain only indicators of the etiology of SBS.

Sensory Irritants: Volatile Organic Compounds

Volatile organic compounds (VOCs) have been strongly suspected to play a role in "sick building syndrome." Although there is a wide range of SBS symptom types, many symptoms appear to be related to sensory irritation (eye, nose and throat irritation and dry, itchy skin), deep pulmonary stress (chest tightness, difficulty breathing), and systemic symptoms (headache, sleepiness, fatigue). Symptoms of high prevalence reported from various epidemiological investigations of SBS are those of sensory irritation. VOCs have been linked with sensory, pulmonary and neurologic responses in sensory science literature. Thus, there is reason to suspect the VOCs.

VOCs are generally defined operationally as those organic compounds with a boiling point range between 50° C and 260° C (World Health Organization, 1989). Complex mixtures of numerous VOCs are found in buildings; concentration and composition of these mixtures vary widely depending upon both the source types and strengths. Over 300 VOCs have been identified in ambient and indoor air (Shah and Singh, 1988), while 50 are reported to be commonly found indoors (Berglund et al., 1986). Many individual VOCs are commonly detected indoors, at concentrations orders of magnitude lower than Threshold Limit Values (TLVs)[1]. Composition of the VOC mixture can vary widely among buildings (Daisey et al., 1994). Finally, sources of VOCs are ubiquitous and

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1. TLVs are occupational exposure limits, "developed as guidelines to assist in the control of health hazards" (American Conference of Governmental Industrial Hygienists, 1992). The guidelines were designed to prevent irritation of eye, nose and throat in nearly all workers of the industrial population (generally healthy, adult males). TLVs are the upper bound of acceptable exposure levels for occupational exposures, and are often used as the upper bound limits for nonindustrial populations, in spite of the recommendations to the contrary by the American Conference of Governmental Industrial Hygienists (ACGIH).

include: humans and their activities (Wang, 1975; Wallace et al., 1989; Clobes et al., 1992), building materials (Berglund et al., 1989), solvents (Lebret et al., 1986), office equipment (Hodgson et al., 1991), carpets (Hodgson et al., 1993), automobile emissions (Daisey et al., 1994), cleaning products (Miksch et al., 1982), dry cleaned clothing (Scheff et al., 1989; Wallace, 1989; Wallace et al., 1989), environmental tobacco smoke (ETS) (Loforth et al., 1989).

Indoor exposure to VOCs in nonindustrial settings is mainly through inhalation, although dermal and oral routes are also experienced. Airborne contaminants are detected by the nose through two systems: olfaction and the common chemical sense. The common chemical sense is the chemical sensitivity of mucosae of the human body. The chemical sensitivity, or more commonly sensory irritation (Alarie, 1973), of the human face and head is mediated by the free endings of the facial trigeminal nerve system. Toxicological experiments on both animals and humans indicate that although interlinked, the olfaction and sensory irritation systems have different functions: olfaction is mainly a sensory system to describe the environment; sensory irritation functions mainly as a warning system.

The warning system of the common chemical sense is evoked via stimulation of the trigeminal nerve, which excites sensations of irritation, burning, tingling, and even freshness (for example menthol) as a sense of pungency. A common example of concurrent odor and pungency stimulation occurs on exposure to household ammonia. Upon opening a bottle of cleaning solution the smell of ammonia is noted, and if the

exposure is close enough to trigger response, a pricking, tingling of the facial skin and a reflexive blinking of the eyes is experienced. Human chamber studies (Cometto-Muniz and Cain, 1992) have shown individuals lacking a sense of smell (anosmics) retain the warning function of the trigeminal nerve system; conversely, individuals with complete destruction of the trigeminal nerve retain the olfaction sense. Investigators are currently exploring the separate odor and pungency thresholds for individual VOCs.

Human exposures to and the role of VOCs as potential sensory irritants have been investigated through controlled human chamber studies, as well as animal (mouse) bioassays and epidemiological studies. Human chamber studies have indicated that individual VOCs (Cometto-Muniz and Cain, 1990), as well as complex mixtures of VOCs (Kjaergaard et al., 1991), elicit irritant sensations at concentrations below Threshold Limit Values (TLVs). Nonindustrial exposures tend to be well below TLV concentrations indicated for individual VOCs.

At issue are influences of multiple VOCs, and low levels of individual VOCs, on associations with symptoms of the nonindustrial working population. In buildings where workers report symptoms, exposures to any individual VOC are typically 100- to 1000-fold below TLVs, although odor thresholds can be reached. Because of this, it has been hypothesized that the total concentration of all the VOCs taken together are a "causative" factor of SBS, and that total VOC (TVOC) can be used as an exposure metric that is related to symptoms.

Total Volatile Organic Compounds

In practice, TVOC generally refers to the sum of the mass concentrations of individual VOCs, exclusive of very volatile compounds and highly reactive compounds like formaldehyde (Hodgson and Wooley, 1992). The definition alludes to the difficulty in capturing either compounds of high volatility which quickly outgas, or compounds that react with either other compounds or adsorb to features of the indoor environment (walls, furnishings) and are lost from the air.

Operationally, TVOC is defined in several ways as no standardized or widely agreed upon method for quantification of TVOC currently exists for indoor air quality. The most typical method to sample for VOCs uses sorbent samples, Tenax-TA (Tenax) alone or a multi-sorbent sampler. Described in detail elsewhere (Hodgson and Girman, 1989), the multi-sorbent sampler collects compounds over a wider volatility range than Tenax alone, and contains Tenax, Ambersorb XE-340, and activated charcoal. Upon thermal desorption from the sampler, the effluent is quantified, typically through either gas chromatography-mass spectrometry (GC-MS) method or simple flame ionization detector (FID) method. Sampling volumes indoors are relatively low, typically 1-3 L collected at a rate of 100 cm^3 min^{-1}.

Sampling

Different sampling methods collect compounds over different volatility ranges. Methods using only the Tenax sampler typically do not capture the VOCs with the lower boiling

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points, below 70° to 80° C (Hodgson and Girman, 1989). Table 2 shows boiling points (°C) for chemicals known to be commonly found indoors. Roughly one third of these chemicals will not be quantified with a method that uses the Tenax sampler alone, instead of the multi-sorbent sampler. Most likely to be unrepresented due to sampling difficulty will be compounds of high volatility (low boiling point) or high reactivity. These latter compounds also tend to be more the irritating compounds.

Charcoal is also sometimes used as a sorbent for collecting VOCs. For this sorbent, VOCs are generally recovered by solvent extraction with carbon disulfide. An aliquot of the solution, rather than the whole sample, is then injected in a gas chromatograph (GC) for analyses. Since Tenax and the multi-sorbent sampler are widely used and were used in this study, the remainder of this discussion focuses on this sampling and analysis method.

Gas Chromatography - Mass Spectrometry (GC-MS)[1]

After collection, a sample is thermally desorbed and introduced to a capillary gas chromatograph (GC) with a sample concentrating and inletting system. The GC is connected via a direct capillary interface to a mass spectrometer (MS) operated to scan a mass range m/z 33-250. Target compounds are quantified using single ion current (SIC) responses from one or two selected ions for each chemical. Overall precision of the method is of the order of 5-10% and often better.

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1. From (Hodgson and Girman, 1989).

TABLE 2. Boiling point (° Celsius) and sampling method for VOCs commonly found indoors (Windholz, 1983)

COMPOUND	Boiling Point (° Celsius)	Sampling Method
Trichlorofluoromethane	24	Multi-Sorbent Sampler
Pentane(n-)	36	Multi-Sorbent Sampler, with Tenax
Dichloromethane	40	
Propanone(2-)	57	
Hexane(n-)	69	
Trichloroethane(1,1,1-)	74	
Ethylacetate	77	
Ethanol	79	
Benzene	80	
Propanol(2-)	83	Tenax or Multi-sorbent Sampler, with Tenax
Trichloroethylene	87	
Heptane(n-)	98	
Pentanal(n-)	102-103	
Toluene	111	
Tetrachloroethylene	121	
Butylacetate(n-)	125-126	
Octane(n-)	126	
Hexanal(n-)	131	
Ethylbenzene	136	
Xylene(m-)	137-140	
Xylene(o-)	137-140	
Xylene(p-)	137-140	
Styrene	145-146	
Nonane(n-)	159	
Trimethylbenzene(1,3,5-)	165	
Trimethylbenzene(1,2,4-)	169-171	
Butoxyethanol(2-)	171-172	
Decane(n-)	174	
Limonene	176	
Benzaldehyde	179	
Undecane(n-)	196	
Phenylethanone(1-)	202	
Dodecane(n-)	216	

The total ion current (TIC) response of the MS is the integrated sum over the chromatographic peak of all compounds. The ratio of the peak height or area on a graph of ion current for a given chemical to the amount of that chemical is defined as the "response factor" for that chemical. A single ion current (SIC) response factor is examined. This response factor is then compared to a chosen reference standard for that chemical. The relative response factor (RRF) is the ratio of SIC response factor to the response factor for a chosen reference standard compound. An average response factor is calculated, based on measured response factors from "reference" chemicals. The "reference" chemicals are chosen to be representative of the remaining compounds. This average response factor from the reference chemicals is applied to the remaining compounds.

Response factors vary. This variability can cause bias in the TVOC estimate if the chosen chemicals are not representative of the remaining compounds. Use of individual response factors for each compound would be more precise; accordingly, precision increases with number of RRS calculated. However, standards for a significant number of individual VOCs do not currently exist. Additionally, this method is time consuming and expensive due to the multiplicity of individual compounds.

Flame Ionization Detector (FID) Method[1]

After thermal desorption, a sample is analyzed using a flame ionization detector (FID). The response from the FID is a single peak as there is no separation of individual peaks

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1. From (Hodgson et al., 1991) and (Hodgson and Wooley, 1992).

using chromatographic separation of compounds. The integrated peak area is calibrated using response factors from a mixture of C_6-C_{12} normal alkane hydrocarbons.

The FID method has best accuracy and precision when used to estimate concentrations of hydrocarbons since carbon is detected by this method. Uncertainty increases when FID is used to estimate compound mass concentrations from mixtures with compounds containing oxygen, nitrogen, or halogens because the presence of these elements changes the response per carbon atom. The advantage to the FID is its relative simplicity, as only a single peak is integrated.

Comparison of GC-MS and FID

The GC-MS and FID methods for measuring TVOC were compared by Hodgson and Wooley (1992). In laboratory experiments, both measurement techniques demonstrated good accuracy and precision between measured and expected TVOC values. Air samples from field experiments analyzed using GC-MS were also compared to those analyzed by FID. The results differ, although not by orders of magnitude. When the results from the two analyses were expressed as hydrocarbon-equivalent concentrations, GC-MS TVOC value was found to be roughly 20% higher on average than FID.

A combined use of both GC-MS and FID provides better characterization of TVOC than either alone. Described by Hodgson and Wooley (1992), the method of combined analysis allows for both FID determination of TVOC and GS-MS analysis of individual VOCs on the same sample. During the thermal concentration of the sample, approximately 8% of

each sample is split off and analyzed directly using a flame ionization detector (FID). GC-MS and FID analyses are then used to estimate TVOC concentrations.

To summarize, reported TVOC levels will vary depending upon sampling and analysis methodologies. Sampling methods that collect VOCs over the widest range of boiling points will more accurately represent air concentrations. As GC-MS and FID analysis methods differ in their individual quantification of VOCs, the choice of reference compounds and determination of average response factors will influence the TVOC value. Additionally, FID gives lower response for compounds with oxygen, nitrogen and halogens. Actual TVOC concentrations will be underestimated if the TVOC mixture contains substantial amounts of compounds with these elements, and only FID is used for analysis.

The ability of the TVOC metric to be associated with symptoms will be attenuated by these differences in analytic methodology. Sampling, recovery and analysis techniques should, therefore, be considered when evaluating associations reported for TVOC exposure metrics.

TVOC as an Exposure Metric

Table 3 describes studies reporting positive associations between SBS symptoms and TVOC, and includes information on study types, symptoms, TVOC values, analysis technique, and references. The table is separated into three broad types of studies: human chamber experiments, studies in complaint buildings, and a study in a noncomplaint

TABLE 3. Summary of information on TVOC levels (mg m^{-3}) *positively* associated with symptoms by chamber experiments, complaint buildings, noncomplaint buildings: Type of study, SBS symptoms, arithmetic mean (range)[a], analysis technique, references

Type of Study	SBS Symptoms *positively* associated with VOCs	TVOC Mean (Range) mg m^{-3}	Analysis Technique	Reference
chamber experiment (sensitive population)	eye, nose, throat irritation	5 & 25 (NA)	pre-set mixture; FID[b]	(Molhave et al., 1986)
chamber experiment (normal, healthy males)	eye, nose, throat irritation	25 (NA)	pre-set mixture; FID[c]	(Otto et al., 1990)
chamber experiment (subjects from previous experiments, paid, friends)	eye, nose irritation significantly reduced well being	8 (NA) 25 (NA)	pre-set mixture; FID[d]	(Molhave et al., 1991)
chamber experiment (healthy adults)	sensory irritation	1.7 (NA)	3 different pre-set mixtures[e]	(Molhave et al., 1993)
complaint buildings (11)	score based on number of SBS symptoms	0.38 (0.05 - 1.4)	charcoal sorbent; GC/ FID[f]	(Norback et al., 1990)
case-control (2 complaint, 2 new, and 2 old buildings)	airway (nasal), general, eye	0.13 (0.07 -0.18)	charcoal sorbent; GC/ FID[g]	(Norback and Torgen, 1990)
longitudinal in a complaint building	headache, eye irritation, throat irritation, erythema, and "itching, stinging, tightness, and feeling of warmth in face without visible rash"	NA (0.05 - 0.36)[h]	porous polystyrene sorbents; GC/ FID[i]	(Berglund et al., 1990; Berglund et al., 1990)
cross-sectional (3 noncomplaint, 5 complaint buildings)	central nervous system	NA 3.0 - 4.0 (ppm)	photoacoustic detector	(Hodgson et al., 1992)
cross-sectional in a noncomplaint building	mucous membrane irritation; central nervous system symptoms	not given	organic vapor analyzer[j]	(Hodgson et al., 1991)

a. NA (not applicable) indicates mean or range not given.

b. Complex mixture; > 90% of the mixture composed of *p*-xylene and *n*-butyl acetate; concentrations measured using toluene equivalents with FID.

c. As in (Molhave et al., 1986).

d. As in (Molhave et al., 1986).

e. No information on analytic technique. Three mixtures of VOCs in 1:1 ratios, based on: 1) low vapor pressure; 2) high vapor pressure, high thermodynamic activity; 3) high vapor pressure, low thermodynamic activity.

f. Analysis performed using GC - FID; *n*-decane response factor used for (C_3-C_{12}), while dodecyl benzene response factor used for ($>C_{12}$).

g. As in (Norback et al., 1990).

h. Samples from exhaust air.

i. Analysis performed using GC - FID and MS; 25 compounds fully identified by their mass spectra and retention times; area of each peak in the chromatograms was integrated; response factor of n-octane.

j. Organic vapor analyzer calibrated to 1,3-butadiene, results expressed as ppm "of four-carbon fragments".

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building. Comparison of the different studies is not straightforward. Different sampling and analysis methodologies are used by each research group, and analysis techniques are not often well described in some of the reports; e.g., lower limits of detection and blanks are not reported, and calibration mixtures are not described. Limitations of each of the studies decrease the validity of results. At the typical TVOC levels found in office settings, investigators have not generally found relationships between worker symptoms and TVOC. Despite these problems, based on the studies reported in Table 3 (discussed below), there is evidence that at high TVOC levels (> 1000 $ug\ m^{-3}$), TVOC appears to have some value as an exposure metric; i.e., relationships to symptoms are observed.

Table 3 begins with the human exposure chamber experiments. Molhave et al. used mixtures of 22 VOCs in fixed ratios to evaluate response; only the total concentration of the mixture varied, the relative ratios of the 22 compounds remained the same. Two compounds, p-xylene and n-butyl acetate, comprised over 90% of the mass of the mixture. The authors reported that compounds and their relative ratios were chosen to be representative of concentrations of VOCs that they had measured in the indoor environment. Subjects were chosen from various populations (see Table 3). The general structure of the experiments was to expose subjects in the chamber for 2.75 hours twice during a day, with one of the two periods being at zero concentration, and the other being at the study exposure level. Measurements of response included both objective and subjective indications. Study designs were double blind. SBS symptoms were positively associated with exposure levels of 1.7 mg m^{-3} or greater.

The first two complaint building studies listed in Table 3 were based on a study of primary schools in Sweden. In 1982, a cross-sectional questionnaire sent to primary schools in Uppsala found that schools with wall-to-wall carpets reported an enhanced prevalence of eye and airway symptoms, face rashes, headache, abnormal tiredness (Norback and Torgen, 1989). A longitudinal study (May 1982 to May 1986) was based on the results from the cross-sectional study. Two buildings from the longitudinal study were chosen for comparison with four control buildings without carpeting (two new and two old primary schools) (Norback and Torgen, 1990). All six schools had been built prior to 1974. Environmental measurements (VOC, temperature, concentrations of respirable dust, CO_2, formaldehyde) were made in November 1986, after the questionnaire study was finished. Exposed and nonexposed groups were compared by symptom frequencies (score of SBS symptoms). Based on regression analyses, concentration of TVOC was related to chronic airway ($p < 0.01$), chronic general ($p < 0.01$), and chronic eye symptoms ($p < 0.05$), but not to chronic skin symptoms. Mean TVOC concentration over all buildings (n=6) was 0.13 mg m^{-3}.

Further questions were pursued by the same researchers in a longitudinal study of 11 complaint buildings (Norback et al., 1990). The study was based on all consecutive cases of sick buildings with more than 10 employees during a three-year period (March 1984 to April 1987). To minimize the influence of air sampling on the questionnaire results, questionnaire investigation was completed prior to exposure measurements. Questionnaires were administered and measurements taken during the heating season

(October to April). Specific temporal and spatial relationships between measurements and questionnaire administration were not described. Total indoor hydrocarbon concentration correlated with a number of SBS symptoms. Geometric mean TVOC concentration over all buildings (n=11) was 0.21 (± 2.6) mg m^{-3}; the highest measured concentration was 1.4 mg m^{-3}.

The last of the complaint studies in Table 3 was a library building in Sweden classified as "sick" by health officials (Berglund et al., 1990; Berglund et al., 1990). TVOC samples were from intake and exhaust air; the latter is reported, based on the assumption that exhaust air is more representative of indoor exposures. Prevalence change over the day (morning frequency - afternoon frequency) of visitors' symptom reports showed a strong linear relationship with the mean concentration of 34 VOCS measured in exhaust air. These symptoms included headache, eye irritation, throat irritation, erythema, and "itching, stinging, tightness, and a feeling of warmth in the face without visible skin rash". TVOC concentration in the exhaust air ranged from 0.05 - 0.36 (mg m^{-3}).

Reports from noncomplaint buildings are rare. The noncomplaint cross-sectional study, listed last in Table 3, was unique in several aspects. Hodgson and colleagues (1991) collected *personal* exposure measurements in a *noncomplaint* building, and found TVOC to be associated with SBS symptoms of mucous membrane irritation. This study is the most indicative of the potential for TVOC as an exposure metric, but there are problems with the sampling and analytical methodologies. Personal exposure measurements more

accurately reflect exposure than area-wide measurements; however, measurements were collected only once at each workstation, and no attempt was made to validate the samples. The sampling and analytical technique was not sufficiently described[1]. Mucous membrane irritation and central nervous system symptoms were reported to be related to concentrations of volatile organic compounds, but TVOC levels were not reported.

Hodgson et al. (1992) surveyed 8 buildings to which they had ready access, including 3 noncomplaint buildings, 3 buildings with minor complaints but no formal investigation, and 2 known complaint buildings. As with the earlier study, personal samples were taken. Sampling and symptom assessment occurred at the same time; 205 office workers participated in the cross-sectional study. TVOC levels were reported by central nervous system levels, and ranged from 3.0 to 4.0 ppm. Although TVOC was related to central nervous system symptoms, the correlations was relatively weak when compared to job stress measurements.

There are specific limitations to each study type discussed above. In the human chamber studies, subjects were from different subpopulations[2], which makes comparison of outcomes (SBS symptoms) across studies difficult. In terms of understanding the relationship between TVOC level and symptom outcome, the choice of VOCs in the mixture was the most important aspect of the human chamber studies, yet two VOCs accounted for greater than 90% of the mass and potency. For these studies, TVOC was less

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1. The "organic vapor analyzer" reported in the study was probably a non-dispersive IR instrument.
2. The subpopulations included: sensitives, normal males, individuals from previous experiments, paid subjects, friends, and normals.

a measure of total exposure to a mix of VOCs than a measure of exposure to *p*-xylene and *n*-butyl acetate. Reports of studies on complaint buildings are numerous; however, these types of studies are most likely to have over-reporting bias. The results from the only noncomplaint building studied were interesting, but the sampling and analytic technique was not clearly specified, and TVOC levels were not reported.

A final issue to consider in summarizing the usefulness of TVOC as an exposure metric is the more general issue of the representativeness of exposure metric (TVOC) to actual exposures. TVOC exposure should be measured close to the time of symptom questionnaire administration. Ideally, personal TVOC measurements should be made; if this is not possible, sampling locations should be carefully selected to be as close as possible to the individuals responding to the questionnaires. Samples taken from intake or exhaust ducts are rarely representative of human exposure, and TVOC samples distanced from questionnaire administration by a year do not accurately reflect potential correlations between exposure and outcome.

Critique of the TVOC Exposure Metric

Studies using the TVOC metric report either positive or no association with symptoms. These inconsistent results are likely to be due to the factors discussed above; for example, failure to measure exposure adequately temporally and spatially, as well as problems with the sampling and analysis methods. The TVOC metric may not include important VOCs, and the compounds being measured may not be those causing symptoms. The more volatile or more reactive chemicals require special sampling methods to accurately

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capture their concentrations. A major problem with the TVOC metric is that different VOCs have different irritancies, or potencies. As a measure of exposure, TVOC does not appropriately incorporate the wide range of biological potencies (physical and chemical reactivity at a physiological level) of these chemicals, but simply sums up concentrations of individual compounds on a mass basis.

A New Approach

Understanding the effect of complex mixtures requires both capturing physiological response using some measure of biological potency, as well as capturing source variability. Previous investigators have not considered individual irritancy of VOCs, nor concurrently examined relationships between various measures of human and animal sensory irritation to pre-select the most significant compounds for analysis. Further, previous researchers have not generally considered in a statistically rigorous manner the high degree to which these compounds are correlated with each other due to being emitted from the same source. The exposure-response relationship between VOCs and symptoms could be hidden due to the complex interactions of numerous, highly correlated compounds. Use of statistical techniques to reduce correlations and disclose the latent sources of VOCs might also help clarify obscured relationships between irritant VOCs and symptoms. Some means is needed to link symptoms to sources of VOCs, e.g., through the use of tracers, in the event that VOCs responsible for symptoms might not have been measured but are correlated to other measured VOCs from that source.

Potency

An alternative approach to the TVOC metric would be test the correlation between a

biologically summarized measure of VOC exposure and reported irritant symptoms. This

approach follows from the irritant effect of individual VOCs reported in the literature, and

from the numerous exposures to and ranges of potencies of individual VOCs. Potencies of

VOCs range over several orders of magnitude (Alarie, 1981). Sources of VOCs can vary,

and thus the composition of the chemical mixtures fluctuate across buildings. Therefore,

an analysis of the relationship between these chemicals and human symptoms should

incorporate some measure of the relative potencies of individual compounds.

Two important problems in addressing irritant potency are that 1) the data for humans is

relatively sparse, and 2) data for some VOCs of interest is lacking. Most of the limited

data on human irritancy response is reported for very high concentrations experienced in

occupational settings. A large body of animal toxicology data has also been generated;

these data show close correlations with standards used for industrial workers (Alarie,

1981). However, acceptable levels of exposure for industrial and nonindustrial workers,

and even the compounds of interest for the two groups, differ. Some VOCs commonly

found indoors do not currently have TLVs (e.g., n-undecane, 2,2,5-trimethylbenzene,

limonene). Finally, a basic problem in toxicology is that extrapolation of high animal

doses to low human exposures is inherently problematic.

Although both animal and human toxicological data on VOC irritant potencies exist and

can be used to select the most irritating compounds, neither source is optimal. Human

irritancy thresholds measured under controlled conditions have been reported for a limited number of VOCs (alcohols, acetates and ketones) (Cometto-Muniz and Cain, 1993). In contrast to irritant potency, a comprehensive compilation of data on human odor thresholds has been developed (Devos et al., 1990), and might be useful in pre-selecting compounds. A third type of data, not previously considered for this type of problem, are simple physical parameters. Researchers have shown that saturated vapor pressure can predict the level at which individual VOCs arouse nasal pungency in mice (Nielsen and Alarie, 1982) and humans (Cometto-Muniz and Cain, 1993). Information on saturated vapor pressure is readily available for almost all VOCs. There is evidence that this simple physical parameter is correlated with physiological responses of irritancy and olfaction (Cometto-Muniz and Cain, 1993). Thus vapor pressure may be useful for estimating values of missing data for animal irritancy response, human irritancy threshold, and human odor threshold.

Summary

No single hypothesis of the etiology of "sick building syndrome" has been conclusively demonstrated, although overall results from several studies justify the theory that some underlying cause exists. Current hypotheses on the cause of SBS incorporate a multifactorial approach, including various chemical and physical environmental measurements as well as psychosocial factors. Due to the sensory irritant nature of individual VOCs, the mass sum of sampled VOCs (the TVOC metric) has been hypothesized to be an important cause of SBS. However, inconsistent results have been

reported from studies linking the TVOC metric to symptom outcomes, and the information from these studies is therefore inconclusive. Problems with sampling and analysis techniques, as well as spatial and temporal positioning of the TVOC samples, may be obscuring the dose-response relationship. Additionally, important VOCs may not be measured and therefore are not included in the TVOC metric. Some method of accounting for missing VOCs needs to be folded into the approach.

Prior research has not attempted to incorporate the biological potencies of individual VOCs, which can range over several orders of magnitude. Potencies could be estimated from animal, human, or simple physical parameters; however, the available data either do not directly address potency (human odor thresholds), or are for the wrong species (mouse bioassays), or are limited in the number of compounds for which information is available (human pungency thresholds). Use of animal data or simple physical parameters to approximate a human metric of exposure is supported by chemical and physical mechanisms; both animal and human kingdoms share the warning system of the common chemical sense as mediated by the trigeminal nerve. However, interpolation of human response from these other data must take into account correlations between measures by chemical class.

Objectives

The major objective of this research was to test the hypothesis that an association exists between some measure of VOC exposure and reported SBS symptoms. This objective had two sub-hypotheses:

- Taking into account biological potency of individual VOCs would increase usefulness of VOC metrics.
- The analysis should incorporate unmeasured VOCs in the event that VOCs not sampled were responsible for symptoms, and missing VOCs emitted by a shared source could be traced using statistical techniques that reduced correlation and disclosed latent sources.

A second objective was to test the hypothesis that animal and human irritancy measures are correlated, and to develop structure-activity relationships with simple physical parameters to estimate missing irritancy data. The third objective was to test the complex hypothesis that a summary measure of VOC vectors, other risk factors, and covariates for each worker would lead to a better prediction of symptom outcome.

The California Healthy Building Study

California Health Building Study (CHBS)[1]

As part of Phase 1 of the California Healthy Building Study (CHBS) (Daisey et al., 1990; Mendell, 1991; Fisk et al., 1993), concentrations of total volatile organic compounds (TVOC) and of 39 individual volatile organic compounds (VOCs) were measured in 12 office buildings in the San Francisco Bay Area in Northern California. The data for the current investigation of the relationships between occupant symptoms and exposures to VOCs were from this larger study. The major objectives of the overall CHBS study were to investigate the prevalence of various occupant symptoms and perceptions of thermal comfort in office buildings selected without regard to worker complaints, and to test hypotheses about

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1. Expanded from previously published material (Daisey et al., 1993).

associations between health symptoms and features of the building, indoor environments, and personal factors. Indoor concentrations of VOCs were measured in each building to characterize indoor air exposures, to investigate inter-office variations in chemical classes and concentrations, and to identify major sources of VOCs. This chapter reports descriptive statistics of the VOCs, reported symptoms, and other microenvironmental measurements.

Sampling Methods

City and county office buildings (excluding jails, hospitals, police stations and fire stations) were chosen from within San Francisco, Alameda, and Contra Costa counties. Smoking within all city and county buildings was prohibited except in specific areas. The selection requirements were: 1) more than 929 square meters of currently occupied office space; 2) at least 45 full-time and at least 10 clerical workers; 3) not containing unusual pollutant sources; 4) no ongoing renovations; and 5) one of three ventilation types: naturally ventilated (NV), mechanically ventilated (MV) with operable windows and no air conditioning, and mechanically ventilated with sealed windows and air conditioning (AC). Permission for the study was given for 3 of 4 eligible MV buildings, 3 of 4 NV buildings, and 6 of 11 AC buildings. No reason for refusal was given for the MV or NV buildings and 1 of the AC buildings; the reason for refusal for 4 of the AC buildings was preexisting tension about health or comfort of the building; the reason for refusal of 1 of the AC buildings was heavy workloads. All eligible buildings to which access was granted were included. Workers within selected study spaces of each building were invited to

participate in the study. Spaces were chosen to be as similar across buildings as possible.

Open study spaces were chosen where possible; in some cases adjoining offices were

included.

Table 4 provides descriptive information on the twelve study buildings; 3 NV, 3 MV and 6

TABLE 4. Characteristics of the buildings selected for the California Health Buildings Study, Limited Subset of Individuals (n=517)

Ventilation Type	Bldg. #	Floor Area (m^2)	Number of Floors	Year Built	Number of VOC Sampling Locations	Number of Eligible Individuals in Building[a]
Natural	1	3,400	10	1964[b]	2	15
	10	2,700	3	1895	3	21
	12	36,000	6	1915	1	33
Mechanical	6	5,400	2	1955	1	39
	9	2,300	4	1954	3	28
	11	36,000	6	1915	1	63
Air Conditioned	2[c]	11,000	9	1978	2	103
	3	19,000	7	1982	1	27
	7	8,600	5	1964	2	65
	8	6,000	4	1964	2	55
	4	3,800	3	1987	2	42
	5	9,000	12	1957	2	26

a. In combining the symptom reporting and VOC data, the original 880 subjects was reduced to a total of 517 (see discussion on page 33).

b. Date rebuilt, originally constructed in 1912.

c. History as a sick building.

AC. The ages of the buildings ranged from 3 to 95 years; 9 out of 12 of the buildings were

built prior to 1970. The climate in the San Francisco Bay area varies substantially over

relatively short distances. For example, an 8°C temperature difference between the east

and west sides of the Berkeley-Oakland Hills is typical. The area to the west of the hills,

designated as moderate, has a Mediterranean climate, while the area east of the hills is

semi-arid-hot and dry during the day, cool at night. Ten of the buildings were located in

the moderate climate area and two of the AC buildings were located in the hot climate

zone. One of the AC buildings in the moderate climate was a classic problem building with a long history of occupant complaints, causes of which were never clearly identified. The buildings were studied between June and September, 1990.

Environmental measurements were made in 32 areas within the 12 study buildings. Indoor locations of VOC samples were chosen to represent exposures of the individuals in the selected study space(s); e.g., samples were placed at breathing zone level for a seated person (1.4 m above the floor) in the center of the study spaces. The VOCs were collected on multisorbent samplers for 8-hour work day periods and were analyzed for TVOC using a flame-ionization detector and for individual compounds using a capillary gas chromatograph-mass spectrometer (Hodgson et al., 1991). The sums of the concentrations of the individual VOCs (ΣVOC) were compared to TVOC reported as μg m^{-3} of hydrocarbons. The lower limits of detection ranged from 0.1 to 0.4 ppb; 8% of the data were below the limit of detection. As the data were highly skewed (9 compounds had geometric standard deviations (GSDs) of 3.0 or greater), geometric rather than arithmetic concentrations were calculated for descriptive purposes and values below the limit of detection were set to one-half the limit of detection for the individual compounds (Hornung and Reed, 1990).

Outdoor samples were also collected and analyzed. Outdoor sample locations were chosen to be removed from possible point sources of VOCs (e.g., building exhaust vent), and to be convenient to an electrical outlet for the sampling device. Where buildings were located in the same geographical area, one outdoor sample served for multiple buildings;

there were three such cases. Outdoor values below the limit of detection were also set to one-half the limit of detection for each compound (Hornung and Reed, 1990).

VOC and Subject Database

Thirty-nine VOCs and 880 subjects were joined at the individual level; however, the joined data were not available for all subjects. For 137 individuals returning questionnaire data, available VOC samples were judged as not adequately representative of exposures. Either VOCs were not sampled in the area in which the individual was located, or the area samples were not considered representative of personal exposures due to lack of close proximity. For a separate set of 226 subjects, questionnaires were not completed during the week of administration, and responses to symptom questions were not appropriately linked in time with VOC sampling. The final joint VOC and symptom database contained 517 individuals located in 12 buildings with 22 VOC samples. The following statistics are based on this subpopulation of the CHBS population.

Microenvironmental Measurements

The microenvironmental samples are summarized in Table 5. The measurements are listed by sampling location. Weekly averages for temperature and relative humidity are reported by building; therefore, multiple sampling locations within a building will have the same measurement. Temperature and relative humidity showed little variation during the week of sampling; temperatures across buildings ranged from 22 - 25 ° Celsius; relative humidity averaged 47 ± 3.4%. Indoor and outdoor CO_2 concentrations were gathered

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TABLE 5. Summary of microenvironmental measurements

Space Number	Building	CO_2 (ppm)	ΔCO_2 (ppm)	Temperature (°C, weekly average)	Relative Humidity (%)	Bacteria, median (cfu m^{-3})	Fungi, median (cfu m^{-3})
11	1	477	132	24	47	264	65
12	1	458	113	24	47	264	65
21	2	413	68	24	43	146	12
22	2	402	57	24	43	146	12
33	3	391	56	23	43	271	20
41	4	541	219	23	43	218	5
42	4	553	231	23	43	218	5
51	5	447	121	24	46	202	14
53	5	486	160	24	46	202	14
61	6	388	66	23	55	150	43
71	7	431	82	25	48	90	10
72	7	433	84	25	48	90	10
81	8	406	57	24	46	121	12
82	8	387	38	24	46	121	12
91	9	394	45	26	47	152	52
93	9	388	39	26	47	152	52
94	9	a	a	26	47	152	52
101	10	378	46	25	52	102	85
102	10	415	83	25	52	102	85
103	10	383	51	25	52	102	85
111	11	374	42	25	47	70	81
121	12	393	61	24	50	164	65

a. CO_2 sample missing.

using one week (40 hour work week) bag samples; the difference between indoor and outdoor CO_2 concentrations (ΔCO_2) is sometimes used as an indicator of occupant-adjusted ventilation. Cultural air borne fungi and bacterial levels were also sampled, and are reported in units of median cfu m^{-3} (Fisk et al., 1993).

Descriptive Statistics: VOCs

Descriptive statistics of VOCs and TVOC were calculated for each building from the average concentrations at the one to four sampling sites within each building. The two sampling areas within building 5, located on the 2nd and 6th floors and designated 5.2 and 5.6, were treated as separate buildings because the two floors had separate ventilation

systems and only one was affected by the presence of liquid-process photocopiers. This gave an effective total of 13 buildings.

Total Volatile Organic Compounds

Geometric mean (GM), geometric standard deviation (GSD) as well as arithmetic mean (AM) and arithmetic standard deviation (SD) are presented in the following tables and figures. As shown in Table 6, the indoor concentrations of TVOC measured in these

TABLE 6. Indoor concentrations of ΣVOCs (μg m^{-3}) and TVOC (μg m^{-3}) and ranges of concentrations[a]

Compound	Geo. Mean ± GSD	Arithmetic Mean ± Std. Deviation	Range of Concentrations
ΣVOC	300 ± 1.4	320 ± 110	150 - 550
TVOC	560 ± 2.3	940 ± 1500	240 - 7,000

a. Averages and ranges for 13 buildings.

northern California office buildings were generally low, ranged from 240 μg m^{-3} to 7,000 μg m^{-3} and, with one exception, were higher than outdoor air concentrations. The highest TVOC values (> 2000 μg m^{-3}) were measured in buildings with liquid-process photocopiers (Buildings 4 and 5.6, see Figure 1). The gas chromatograms of the air samples from these buildings were dominated by a characteristic mixture of C_{10}-C_{11} isoparaffinic hydrocarbons. If these values are excluded, the median TVOC concentration was 460 μg m^{-3} for the remaining buildings. The impacts of such office equipment on TVOC levels has been reported previously (Tsuchiya and Stewart, 1990; Hodgson et al., 1991; Wolkoff et al., 1993). Figure 1 clearly shows the impact of two sites on the TVOC values of this data set.
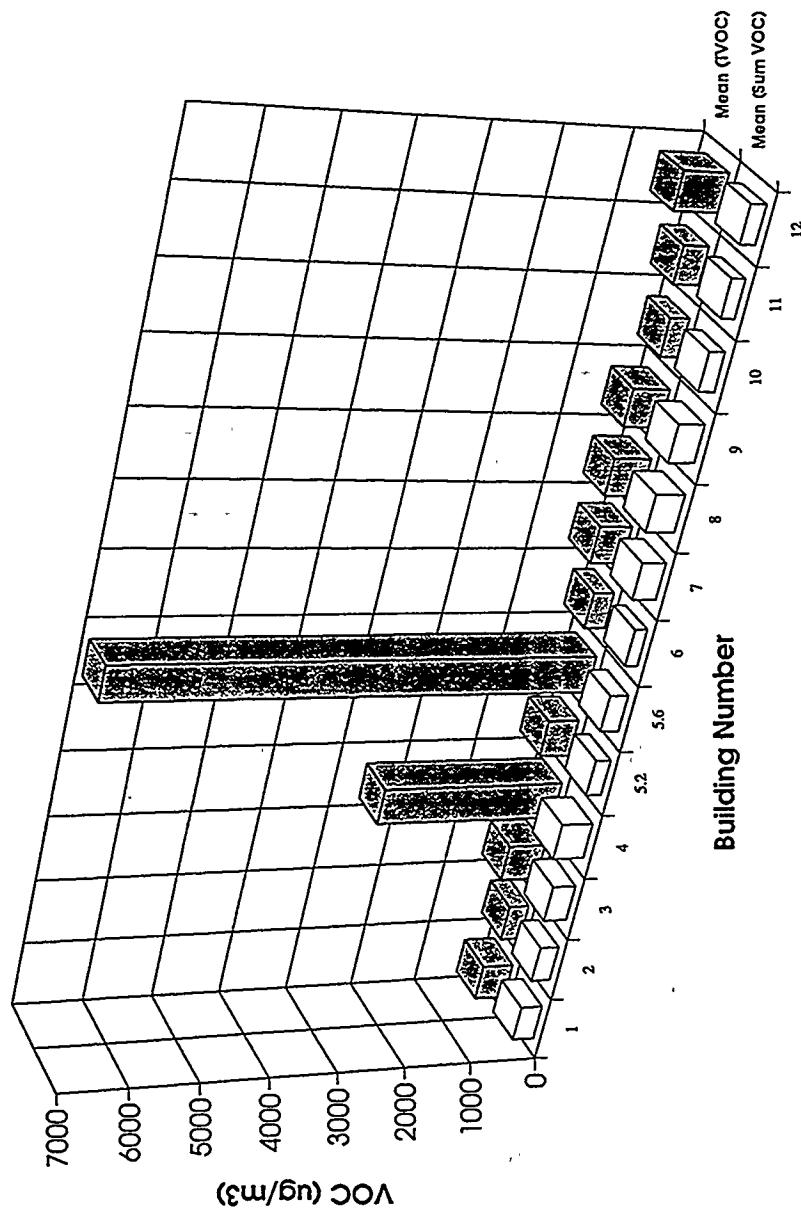
FIGURE 1. Mean sum of VOC (μg m^{-3}) versus mean TVOC (μg m^{-3}) by Building

Table 7 presents ΣVOC and TVOC by ventilation type, while Table 8 presents ΣVOC and

TABLE 7. Geometric mean ± standard deviation and arithmetic mean ± standard deviation of ΣVOCs (μg m⁻³) and TVOC (μg m⁻³), by ventilation type and exclusive of Buildings 4 and 5.6

Compound	Air Conditioning	Mechanical	Natural
Geometric Mean ± Geometric Standard Deviation			
ΣVOC	320 ± 1.4	280 ± 1.5	250 ± 1.4
TVOC	440 ± 1.3	440 ± 1.3	370 ± 1.5
Arithmetic Mean ± Standard Deviation			
ΣVOC	330 ± 110	300 ± 130	260 ±85
TVOC	460 ± 120	450 ±120	400 ± 170

TABLE 8. ΣVOCs (μg m⁻³), TVOC (μg m⁻³), and ΣVOC as a percent of TVOC, by building

Building	ΣVOC	TVOC	Percent[a]
1	325	462	70
2	278	303	92
3	343	551	62
4	467	2662	18
5.2	223	462	48
5.6	277	6972	4
6	174	304	57
7	346	486	71
8	428	537	80
9	379	536	71
10	229	275	84
11	202	362	56
12	225	650	35

a. ΣVOC/TVOC * 100%

TVOC by building. These two tables demonstrate that, except for the buildings with the

liquid-process photocopiers, levels of TVOC were similar across building and ventilation type. The GM values of TVOC (excluding the buildings with the liquid-process photocopiers) did not differ significantly among the three types of building ventilation: 370 $\mu g\, m^{-3}$ ($\pm$ 1.5) (NV); 440 $\mu g\, m^{-3}$ ($\pm$ 1.3) (MV); 440 $\mu g\, m^{-3}$ ($\pm$ 1.3) (AC). Concentrations of TVOC in Building 2, the complaint building, did not differ significantly from concentrations in other buildings. The sums of the 39 individual VOCs (ΣVOC) which were quantified accounted for 35% to 90% of the TVOC values, as shown in Table 8. This is compared to buildings with liquid-process photocopiers (Buildings 4 and 5.6), where ΣVOC accounted for only 18% and 4%, respectively, of TVOC. For these buildings, ΣVOC was not a good representation of TVOC level.

Individual VOCs

Table 9 presents GM, GSD, arithmetic mean, arithmetic standard deviation, and ranges of individual VOCs for all buildings. Overall, GMs were less than 7 ppb for all compounds with the exception of ethanol at 22 ppb. As is typical for environmental measurements, the compounds were observed to be lognormally distributed. The spread of the distributions is demonstrated by the size of the error bars shown in Figure 2; data were skewed (one fourth of the compounds had GSDs of 3.0 or greater). Individual GMs ($\pm$ GSD) by ventilation type are listed in Table 10. When calculated by ventilation type and plotted on a log scale as shown in Figure 3, the spread increased slightly, but still remained below 50

TABLE 9. Five chemical classes, geometric mean ± standard deviation, arithmetic mean ± standard deviation, and range of concentrations of individual VOC (ppb) in San Francisco Bay Area office buildings

Compounds	CLASS[a]	Geometric Mean ± Geo. Std. Deviation	Arithmetic Mean ± Std. Deviation	Range of Concentrations
Benzaldehyde	Oxidized HC	0.50 ± 2.0	0.59 ± 0.26	< 0.1 ± 1.1
Benzene	Aromatic	1.0 ± 2.7	1.3 ± 0.76	< 0.1 ± 2.7
2-Butoxyethanol	Oxidized HC	1.5 ± 3.9	3.4 ± 5.7	< 0.4 ± 27
n-Butyl acetate	Oxidized HC	0.22 ± 2.7	0.31 ± 0.21	< 0.1 ± 0.88
n-Decane	Alkane	0.46 ± 3.3	0.76 ± 0.78	< 0.1 ± 3.9
Dichloromethane	Chlor HC	0.49 ± 6.7	3.1 ± 8.9	< 0.1 ± 41
n-Dodecane	Alkane	1.7 ± 3.0	3.7 ± 6.4	0.44 ± 24
Ethanol	Oxidized HC	22 ± 1.8	27 ± 25	8.7 ± 130
Ethyl acetate	Oxidized HC	0.39 ± 3.2	0.70 ± 0.82	< 0.1 ± 3.0
Ethylbenzene	Aromatic	0.51 ± 1.5	0.55 ± 0.21	0.29 ± 0.98
2-Ethyltoluene	Aromatic	0.46 ± 1.7	0.52 ± 0.24	0.21 ± 0.98
3/4-Ethyltoluene	Aromatic	0.77 ± 1.6	0.86 ± 0.42	0.42 ± 1.7
n-Heptane	Alkane	0.40 ± 1.4	0.43 ± 0.13	0.16 ± 0.72
n-Hexanal	Oxidized HC	0.51 ± 1.9	0.61 ± 0.44	0.20 ± 1.9
n-Hexane	Alkane	0.56 ± 2.5	0.74 ± 0.44	< 0.1 ± 1.6
Limonene	Terpene	1.2 ± 2.5	1.6 ± 1.3	< 0.2 ± 5.0
Methylcyclohexane	Alkane	0.38 ± 1.6	0.42 ± 0.17	0.13 ± 0.76
Methylcyclopentane	Alkane	0.47 ± 1.7	0.54 ± 0.29	0.20 ± 1.2
3-Methylhexane	Alkane	0.34 ± 1.5	0.37 ± 0.16	0.18 ± 0.71
n-Nonane	Alkane	0.30 ± 2.7	0.48 ± 0.59	< 0.1 ± 2.5
n-Octane	Alkane	0.26 ± 2.6	0.40 ± 0.43	< 0.1 ± 1.9
n-Pentanal	Oxidized HC	0.19 ± 3.7	0.42 ± 0.52	< 0.1 ± 1.7
n-Pentane	Alkane	2.7 ± 2.1	3.5 ± 2.5	0.46 ± 8.9
1-Phenylethanone	Oxidized HC	1.0 ± 1.3	1.1 ± 0.33	0.67 ± 1.9
2-Propanol	Oxidized HC	2.3 ± 4.2	6.1 ± 13	< .2 ± 62
2-Propanone[b]	Oxidized HC	4.7 ± 1.5	5.1 ± 2.5	2.7 ± 11
Styrene	Aromatic	0.42 ± 1.9	0.49 ± 0.21	< 0.1 ± 0.87
Tetrachloroethylene	Chlor HC	0.44 ± 2.7	0.64 ± 0.51	< 0.1 ± 1.8
Toluene	Aromatic	2.9 ± 1.8	3.5 ± 3.1	0.77 ± 17
1,1,1-Trichloroethane	Chlor HC	4.1 ± 3.8	7.9 ± 8.9	0.10 ± 41
Trichloroethene	Chlor HC	2.0 ± 2.2	2.6 ± 1.7	0.31 ± 6.9
Trichlorofluoromethane[c]	Chlor HC	0.89 ± 2.2	1.8 ± 1.5	0.30 ± 6.3
1,2,3-Trimethylbenzene	Aromatic	0.30 ± 3.0	0.45 ± 0.34	< 0.1 ± 1.1
1,2,4-Trimethylbenzene	Aromatic	0.79 ± 1.7	0.89 ± 0.45	0.31 ± 1.7
1,3,5-Trimethylbenzene	Aromatic	0.36 ± 2.0	0.42 ± 0.17	< 0.1 ± 0.69
2,2,5-Trimethylhexane	Alkane	0.14 ± 1.6	0.16 ± 0.07	< 0.1 ± 0.31
n-Undecane	Alkane	1.2 ± 3.0	1.9 ± 2.3	< 0.1 ± 11
m/p-Xylene	Aromatic	2.1 ± 1.6	2.3 ± 1.1	0.93 ± 4.6
o-Xylene	Aromatic	0.66 ± 1.6	0.73 ± 0.32	0.30 ± 1.4

a. Alkane = Alkanes; Aromatic = Aromatics; Oxidized HC = Oxidized Hydrocarbons; Chlor HC = Chlorinated hydrocarbons; Terpene = terpenes (limonene).

b. 2-Propanone is commonly referred to as acetone.

c. Trichlorofluoromethane is commonly referred to as freon, and more specifically as freon-11 (F-11).
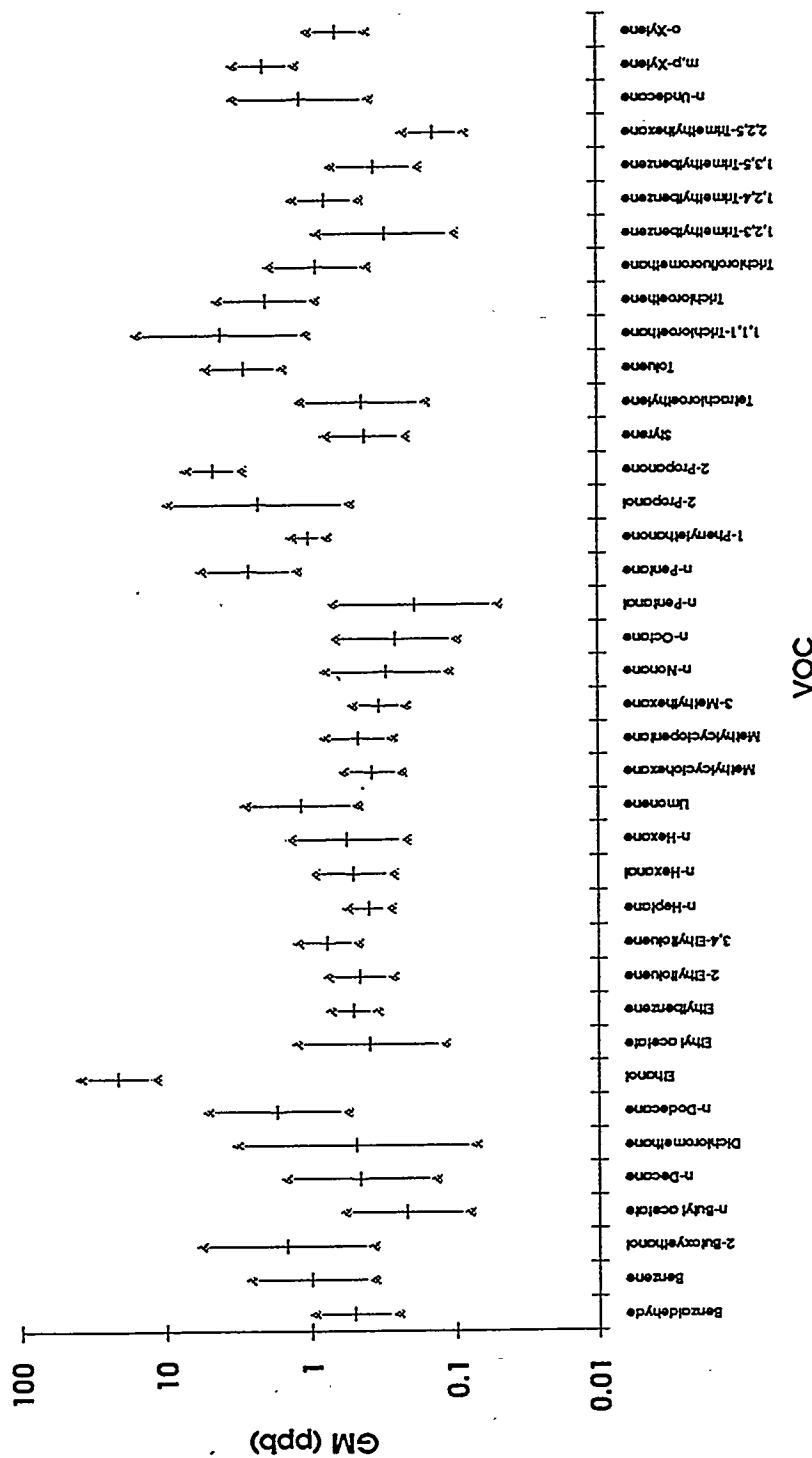
FIGURE 2. Geometric mean (log scale) with one standard deviation above and below for CHBS VOCs

TABLE 10. Geometric mean and geometric standard deviation (ppb) by ventilation type

Compounds	Air Conditioned	Mechanical	Natural
Benzaldehyde	0.57 ± 1.5	0.37 ± 2.2	0.39 ± 2.8
Benzene	0.79 ± 3.2	0.53 ± 5.3	1.2 ± 1.7
2-Butoxyethanol	1.2 ± 4.3	3.2 ± 2.3	1.6 ± 6.7
n-Butyl acetate	0.16 ± 3.2	0.42 ± 1.1	0.24 ± 2.4
n-Decane	0.3 ± 4.7	0.62 ± 1.3	0.7 ± 2.0
Dichloromethane	0.48 ± 9.5	0.17 ± 3.5	1.3 ± 2.1
n-Dodecane	2.2 ± 3.9	1.7 ± 1.3	1.3 ± 2.5
Ethanol	23 ± 1.3	11 ± 1.5	22 ± 1.9
Ethyl acetate	0.72 ± 3.1	0.43 ± 1.1	0.14 ± 2.7
Ethylbenzene	0.52 ± 1.4	0.62 ± 1.4	0.39 ± 1.4
2-Ethyltoluene	0.38 ± 1.6	0.38 ± 1.9	0.51 ± 1.58
3/4-Ethyltoluene	0.78 ± 16	0.72 ± 2.1	0.58 ± 1.3
n-Heptane	0.37 ± 1.5	0.42 ± 1.6	0.38 ± 1.4
n-Hexanal	0.53 ± 2.2	0.55 ± 1.5	0.58 ± 1.3
n-Hexane	0.47 ± 3.3	0.66 ± 2.3	0.51 ± 1.2
Limonene	1.6 ± 2.9	0.65 ± 1.2	1.0 ± 2.3
Methylcyclohexane	0.34 ± 1.6	0.38 ± 1.5	0.38 ± 1.7
Methylcyclopentane	0.47 ± 1.5	0.4 ± 2.7	0.36 ± 1.5
3-Methylhexane	0.33 ± 1.5	0.37 ± 1.8	0.28 ± 1.4
n-Nonane	0.22 ± 3.3	0.46 ± 1.2	0.36 ± 1.9
n-Octane	0.23 ± 2.2	0.43 ± 1.4	0.19 ± 3.4
n-Pentanal	0.31 ± 3.7	0.33 ± 4.2	0.13 ± 3.5
n-Pentane	2.7 ± 2.3	3.3 ± 2.5	1.5 ± 1.6
1-Phenylethanone	1.1 ± 1.9	1.1 ± 1.1	0.87 ± 1.1
2-Propanol	3.6 ± 4.4	0.67 ± 3.3	1.4 ± 5.7
2-Propanone	5.5 ± 1.5	3.6 ± 1.3	4.7 ± 1.6
Styrene	0.38 ± 1.1	0.13 ± 3.7	0.54 ± 1.4
Tetrachloroethylene	0.35 ± 3.0	0.12 ± 3.5	0.93 ± 1.4
Toluene	3.3 ± 1.8	1.6 ± 2.8	2.2 ± 1.6
1,1,1-Trichloroethane	3.7 ± 5.4	6.4 ± 1.7	2.8 ± 2.7
Trichloroethene	1.9 ± 2.7	1.6 ± 1.4	2.3 ± 2.1
Trichlorofluoromethane	1.2 ± 2.4	0.56 ± 2.4	0.53 ± 1.9
1,2,3-Trimethylbenzene	0.45 ± 1.6	0.46 ± 1.9	0.07 ± 2.2
1,2,4-Trimethylbenzene	0.76 ± 1.7	0.61 ± 2.5	0.66 ± 1.4
1,3,5-Trimethylbenzene	0.31 ± 2.5	0.46 ± 1.4	0.35 ± 1.2
2,2,5-Trimethylhexane	0.16 ± 1.7	0.15 ± 1.4	0.1 ± 1.4
n-Undecane	1.2 ± 3.9	0.96 ± 3.1	0.87 ± 2.5
m/p-Xylene	2.0 ± 1.6	2.8 ± 1.51	1.6 ± 1.4
o-Xylene	0.65 ± 1.6	0.78 ± 1.6	0.51 ± 1.5
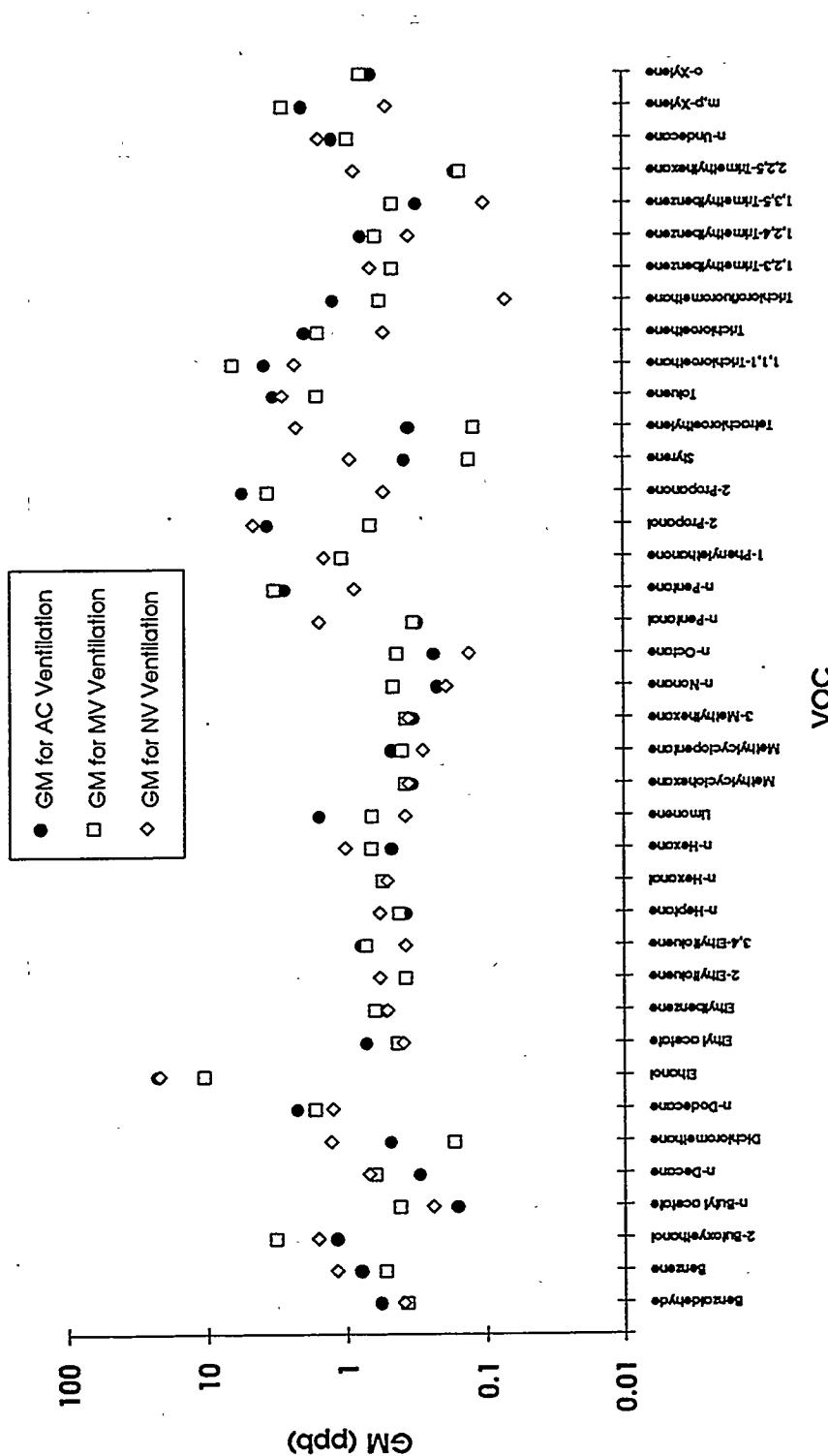
FIGURE 3. Geometric mean (log scale) of CHBS VOCs by ventilation type

ppb. Table 11 presents GM, GSD, arithmetic mean, arithmetic standard deviation, and

TABLE 11. Geometric means ± standard deviations, arithmetic means ± standard deviations, and ranges of concentrations of individual VOC ($ug\ m^{-3}$)

Compounds	GM ± GSD	Mean ± Std. Dev.	Ranges of Concentrations
Benzaldehyde	2.2 ± 2.0	2.6 ± 1.1	0.22 - 4.9
Benzene	3.2 ± 2.7	4.3 ± 2.4	0.16 - 8.7
2-Butoxyethanol	7.2 ± 3.9	16 ± 28	0.97 - 130
n-Butyl acetate	1.0 ± 2.7	1.5 ± 1.0	0.24 - 4.2
n-Decane	2.7 ± 3.3	4.4 ± 4.6	0.29 - 23
Dichloromethane	1.7 ± 6.7	11 ± 31	0.17 - 142
n-Dodecane	12 ± 3.0	26 ± 45	3.1 - 170
Ethanol	41 ± 1.8	51 ± 47	16 - 240
Ethyl acetate	1.4 ± 3.2	2.5 ± 3.0	0.18 - 10.9
Ethylbenzene	2.2 ± 1.5	2.4 ± 0.9	1.2 - 4.3
2-Ethyltoluene	2.3 ± 1.7	2.6 ± 1.2	1.1 - 4.8
3/4-Ethyltoluene	3.8 ± 1.6	4.3 ± 2.1	2.1 - 8.3
n-Heptane	1.7 ± 1.4	1.8 ± 0.5	0.65 - 2.9
n-Hexanal	2.1 ± 1.9	2.5 ± 1.8	0.41 - 7.9
n-Hexane	2.0 ± 2.5	2.6 ± 1.5	0.18 - 5.7
Limonene	6.5 ± 2.5	9.0 ± 7.2	0.56 - 28
Methylcyclohexane	1.5 ± 1.6	1.7 ± 0.7	0.54 - 3.1
Methylcyclopentane	1.6 ± 1.7	1.9 ± 1.0	0.67 - 4.1
3-Methylhexane	1.4 ± 1.5	1.5 ± 0.7	0.72 - 2.9
n-Nonane	1.6 ± 2.7	2.5 ± 3.1	0.26 - 13
n-Octane	1.2 ± 2.6	1.9 ± 2.0	0.23 - 9.1
n-Pentanal	0.7 ± 3.7	1.5 ± 1.8	0.18 - 5.9
n-Pentane	7.9 ± 2.1	10.3 ± 7.5	1.4 - 26
1-Phenylethanone	5.1 ± 1.3	5.3 ± 1.6	3.3 - 9.5
2-Propanol	5.7 ± 4.2	15 ± 31	0.25 - 150
2-Propanone	11 ± 1.5	12 ± 6	6.5 - 27
Styrene	1.8 ± 1.9	2.1 ± 0.9	0.21 - 3.7
Tetrachloroethylene	2.9 ± 2.7	4.3 ± 3.5	0.34 - 12
Toluene	11 ± 1.8	13 ± 12	2.91 - 63
1,1,1-Trichloroethane	22 ± 3.8	43 ± 49	0.54 - 220
Trichloroethene	11 ± 2.2	14 ± 9.2	1.6 - 37
Trichlorofluoromethane	5.0 ± 2.2	7.1 ± 8.2	1.7 - 35
1,2,3-Trimethylbenzene	1.5 ± 3.0	2.2 ± 1.7	0.25 - 5.6
1,2,4-Trimethylbenzene	3.9 ± 1.7	4.4 ± 2.2	1.5 - 8.6
1,3,5-Trimethylbenzene	1.8 ± 2.0	2.1 ± 0.8	0.25 - 3.4
2,2,5-Trimethylhexane	0.8 ± 1.6	0.8 ± 0.4	0.26 - 1.7
n-Undecane	7.4 ± 3.0	12 ± 15	0.32 - 71
m/p-Xylene	9.2 ± 1.6	10 ± 4.8	4.1 - 20
o-Xylene	2.9 ± 1.6	3.2 ± 1.4	1.3 - 5.9

ranges of individual VOCs for all buildings in units of $ug\ m^{-3}$.

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Chemical Composition of the Mixtures

For examination of chemical composition variability among buildings, VOCs were grouped into five chemical classes: alkanes, aromatics, oxidized hydrocarbons, chlorinated hydrocarbons and terpene (limonene). Although there was relatively little variation in the overall levels of TVOC and ΣVOC among these buildings (excepting Buildings 4 and 5.6), there was considerable variation in the chemical composition of the VOC mixtures, as shown in Figure 4.

The oxidized hydrocarbons accounted for the greatest proportion of the VOCs for all of the buildings. Ethanol contributed substantially to the oxidized hydrocarbon class in many buildings, with concentrations ranging from 8.7 to 130 ppb. Concentrations of chlorinated hydrocarbons were highly variable among buildings and even within buildings, ranging from a few percent of the sum of the VOCs to as much as one-third. In seven of the buildings (2, 5.2, 5.6, 6, 8, 10, and 12), the chlorinated hydrocarbons were the second most abundant class of VOCs. For six of the buildings (1, 3, 4, 7, 9, and 11), the alkanes or aromatic hydrocarbons were the second most abundant class of VOCs. On a mass basis, the pattern was similar. The oxidized hydrocarbons were the first most abundant class in all buildings. The chlorinated hydrocarbons were the second most abundant class of VOCs in six buildings (2, 5.2, 5.6, 6, 8, 10, and 12). Aromatic hydrocarbons or alkanes were the second or third most abundant class of VOCs in all buildings. Terpenes accounted for the smallest fraction of the total in all of the buildings on both molar and mass basis; however, this class consists of a single quantified compound, limonene.
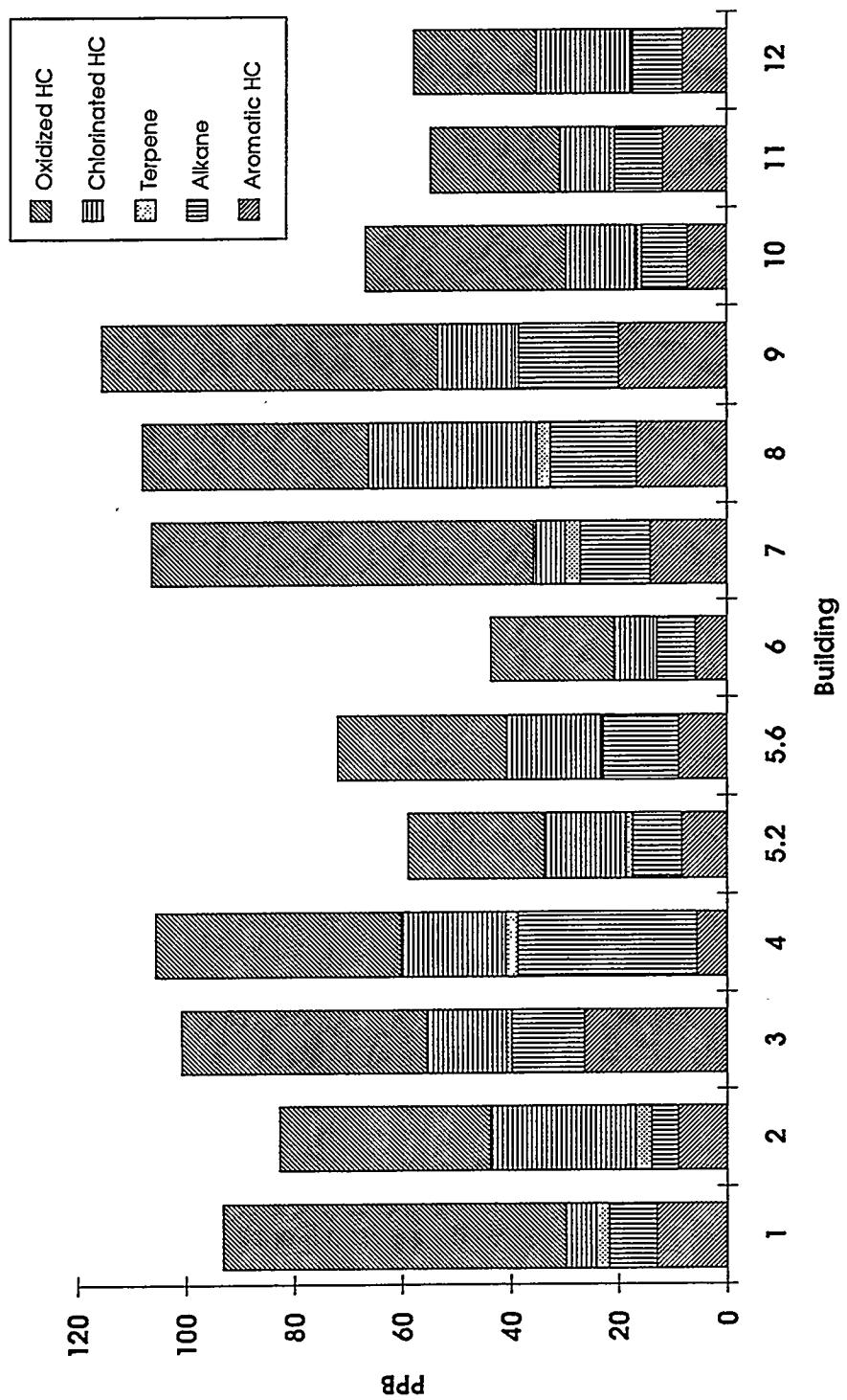
FIGURE 4. Average concentrations of five chemical classes of VOCs in 12 Northern California buildings

Figure 5 presents the variation in chemical class across three different ventilation types. Although there were substantial variations in chemical composition of the VOCs across buildings, the average chemical class concentrations were only slightly elevated in air conditioned buildings. Concentrations of chlorinated hydrocarbons in air conditioned buildings (20 ppb) were two-fold greater than those in mechanically and naturally ventilated buildings, both at 12 ppb. Concentrations of oxidized hydrocarbons were equivalent across NV (43 ppb), MV (47 ppb), and AC (45 ppb) buildings. For alkanes, both AC and MV buildings were equivalent and above NV buildings. Concentrations of terpene (limonene, only) were low overall.

Indoor/Outdoor (I/O) Ratios

To identify major VOC sources common to the buildings, the indoor/outdoor (I/O) ratios were first examined. Outdoor samples were collected for all buildings; however, as the outdoor sample for Building 6 was lost in analysis, ratios were examined for only 12 out of 13 buildings. Outdoor GMs, GSDs, arithmetic means and standard deviations, ranges, and ranges of I/O ratios are shown in Table 12. These values reflect the low overall ambient levels of the VOCs across the San Francisco Bay Area.

The uncertainty of individual values was approximately ± 25%. Propagation of uncertainty in error analysis gives 1 ± 0.35 as the estimated uncertainty in the ratios. VOCs for which the I/O ratio was greater than 1.35 for 8 or more of the buildings were identified as coming predominantly from indoor sources. VOCs for which the I/O ratio was less than or equal to 1.35 for 8 or more of the buildings were identified as coming

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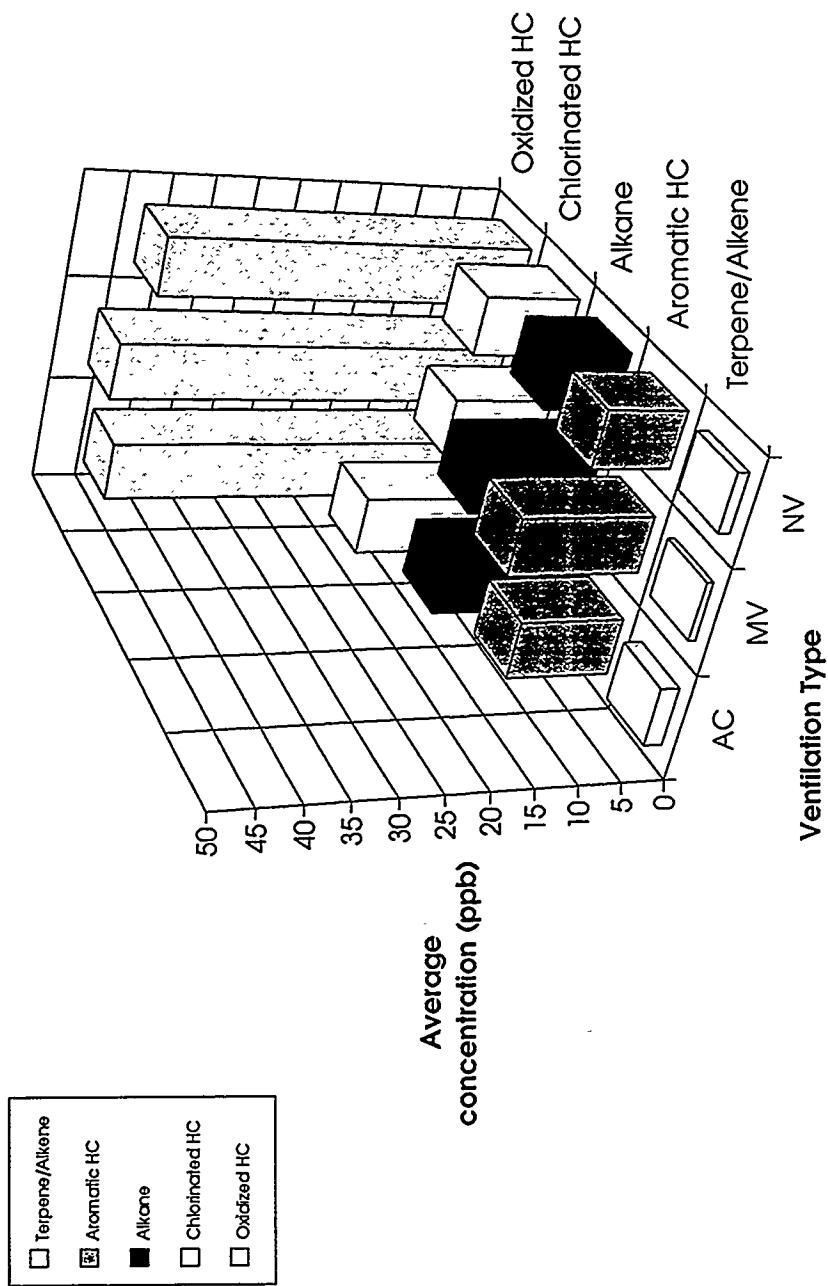
FIGURE 5. Average concentration of five chemical classes by ventilation type

TABLE 12. Geometric means ± standard deviations, arithmetic means ± standard deviations, and ranges of outdoor concentrations (ppb), and ranges of I/O ratios

Compound	Geo. Mean ± GSD	Arithmetic Mean ± Std. Deviation	Range of Concentrations (ppb)	Range of I/O Ratios[a]
Benzaldehyde	3.1 ± 3.4	5.4 ± 4.6	0.44 - 12	0.03 - 1.3
Benzene	1.0 ± 2.8	1.5 ± 1.2	0.22 - 3.1	0.32 - 4.2
2-Butoxyethanol	0.39 ± 5.9	3.2 ± 8.0	< 0.4 - 21	0.17 - 21
n-Butyl acetate	0.08 ± 2.3	0.12 ± 0.12	< 0.1 - 0.32	0.20 - 14
n-Decane	0.43 ± 2.9	0.59 ± 0.36	< 0.1 - 0.97	0.07 -4.0
Dichloromethane	0.21 ± 4.5	0.48 ± 0.58	< 0.1 - 1.5	1.0 - 47
n-Dodecane	0.37 ± 4.2	0.67 ± 0.60	< 0.1 - 1.7	0.27 - 110
Ethanol	2.0 ± 6.6	4.9 ± 5.4	< 0.1 - 15	1.6 - 380
Ethyl acetate	0.09 ± 2.8	0.16 ± 0.18	< 0.1 - 0.48	0.94 - 60
Ethylbenzene	0.39 ± 1.8	0.46 ± 0.32	0.23 - 1.0	0.51 - 2.5
2-Ethyltoluene	0.26 ± 3.4	0.42 ± 0.34	< 0.1 - 0.86	0.64 - 7.1
3/4-Ethyltoluene	0.63 ± 1.8	0.74 ± 0.53	0.36 - 1.8	0.45 - 2.5
n-Heptane	0.29 ± 1.8	0.34 ± 0.19	0.11 - 0.69	0.50 - 2.2
n-Hexanal	0.15 ± 2.0	0.19 ± 0.16	< 0.2 - 0.51	1.0 - 19
n-Hexane	0.27 ± 3.8	0.51 ± 0.57	< 0.1 - 1.7	0.23 - 18
Limonene	0.22 ± 2.7	0.34 ± 0.35	< 0.2 - 1.0	0.69 - 22
Methylcyclohexane	0.22 ± 3.1	0.34 ± 0.31	< 0.1 - 0.89	0.63 - 5.9
Methylcyclopentane	0.32 ± 2.2	0.44 ± 0.42	0.18 - 1.2	0.49- 2.5
3-Methylhexane	0.28 ± 1.8	0.34 ± 0.24	0.17 - 0.78	0.43 - 2.4
n-Nonane	0.33 ± 1.4	0.34 ± 0.10	0.23 - 0.48	0.13 - 8.3
n-Octane	0.11 ± 2.2	0.14 ± 0.10	< 0.1 - 0.30	0.45 - 11
n-Pentanal	0.06 ± 1.3	0.06 ± 0.02	< 0.1 - 0.10	1.0 - 33
n-Pentane	1.4 ± 4.9	2.6 ± 2.8	< 0.1 - 8.5	0.37 - 39
1-Phenylethanone	4.7 ± 3.0	7.0 ± 5.5	0.73 - 15	0.60 - 1.2
2-Propanol	0.31 ± 5.6	1.6 ± 3.6	< 0.2 - 9.8	0.24 - 78
2-Propanone	1.9 ± 2.4	2.5 ± 2.0	0.40 - 6.7	0.85 - 8.9
Styrene	0.16 ± 3.4	0.29 ± 0.28	< 0.1 - 0.70	0.65 - 13
Tetrachloroethylene	0.24 ± 4.6	0.54 ± 0.64	< 0.1 - 1.8	0.73 - 2.8
Toluene	2.0 ± 2.2	2.6 ± 1.9	0.66 - 5.7	0.61 - 5.2
1,1,1-Trichloroethane	0.94 ± 2.1	1.2 ± 1.0	0.44 - 3.4	0.41 - 22
Trichloroethene	0.16 ± 3.0	0.25 ± 0.21	< 0.1 - 0.55	2.2 - 84
Trichlorofluoromethane	0.43 ± 3.0	0.64 ± 0.52	< 0.1 - 1.5	0.72 - 17
1,2,3-Trimethylbenzene	0.13 ± 3.6	0.27 ± 0.35	< 0.1 - 0.98	0.47 - 14
1,2,4-Trimethylbenzene	0.61 ± 2.1	0.78 ± 0.59	0.24 - 1.8	0.45 - 2.7
1,3,5-Trimethylbenzene	0.23 ± 3.0	0.34 ± 0.24	< 0.1 - 0.69	0.62 - 9.7
2,2,5-Trimethylhexane	0.10 ± 1.7	0.12 ± 0.05	< 0.1 - 0.19	0.42 - 6.3
n-Undecane	1.55 ± 2.8	2.8 ± 4.2	0.52 - 12	< 0.1 - 5.9
m/p-Xylene	1.4 ± 2.3	1.9 ± 1.6	< 0.1 - 4.8	0.50 - 3.7
o-Xylene	0.46 ± 2.2	0.60 ± 0.49	0.18 - 1.5	0.53 - 3.3

a. Building # 6 omitted due to loss of outdoor air samples

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predominantly from outdoor sources. The remainder were classified as coming from

mixed indoor and outdoor sources. Those VOCs coming predominantly from indoor or

from outdoor sources are shown in Table 13 grouped by categories of known indoor

TABLE 13. VOCs categorized by source types across buildings and grouped by possible sources

Predominantly from Indoor Sources (I/O >1.35)
Cleaning/Degreasing: dichloromethane, trichloroethene, 1,1,1-trichloroethane
Bioeffluents/BuildingMaterial: ethanol, 2-propanol, 2-propanone
Consumer Products/Building Materials: n-dodecane, n-pentanal, n-hexanal, limonene
Predominantly from Outdoor Sources (I/O <= 1.35)
Motor Vehicle Emissions: benzene, m/p-xylene, o-xylene, 2-ethyltoluene, 3/4-ethyltoluene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, n-pentane, 3-methylhexane
Dry Cleaning: tetrachloroethylene
Other: n-decane, n-nonane

sources.

Benzaldehyde and 1-phenylethanone are known breakdown products of Tenax, one of the

sampling sorbents, and can be produced by reactions of oxidants with Tenax (Pellizzari et

al., 1984). These compounds are suspected to be, in part, indirect indicators of NO_2 and

ozone concentrations, which were not measured in this study. Both benzaldehyde and 1-

phenylethanone show I/O ratios less than 1.35, as would be expected for an ozone-induced

sampling artifact.

Factor Analysis

Factor analysis with orthogonal (varimax) rotation (Norusis, 1990) was used as an

exploratory[1] technique on sub-sets of the VOC data, with and without ΔCO_2, as a means

of identifying sources of VOCs common to these buildings. Factor analysis is a statistical

tool especially useful for investigating relationships between the numerous highly

correlated compounds found in VOC mixtures (Lebret et al., 1986; Noma et al., 1988;

Ulfvarson et al., 1992). The statistical technique is designed to convert multiple, highly

correlated variables to a reduced number of linearized sums, or vectors, referred to as

factors. These factors retain the information from the original data but are uncorrelated

with each other. The specific goal of factor analysis is to test the hypothesis that an

underlying pattern of relationships exists among multiple independent variables, and to

determine whether the many variables can be "reduced" to the smaller number of

underlying patterns:

> "The purpose of factor analysis is to describe, if possible, the covariance relationships among many variables in terms of a few underlying, but observable, random quantities called factors. If variables can be grouped by their correlations, then a particular group of variables will be highly correlated among themselves, but have small correlations with variables of another group. Therefore, it is possible to assume that each group of variables represents a single underlying construct, or factor, that is responsible for the observed correlation."(Johnson and Wichern, 1988, page 401)

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1. Factor analysis is used to develop the structure and assess the fit between data and model where there are hypotheses about underlying structures. However, if there are no *a priori* hypotheses, a related technique, principal component analysis, is often a more appropriate strategy (Tabachnick and Fidell, 1989). Mathematical handling of principal component analysis is less complex and more empirical than factor analysis. Therefore, factor analysis is used herein specifically in an exploratory manner, and principal component analysis will be discussed and used in later chapters for data analysis.

These goals are accomplished through numerical algorithms that use linear algebra to iteratively generate factors. The algorithms are designed to construct factors with the following properties:

- the variance of the first factor is greatest; the variance of the second factor is next; and so on; and,
- each factor is uncorrelated with the others.

An indication of the strength of the linear association among the original variables is the *communality*. The communality is that proportion of the variance of the ith variable contributed by all of the factors, or, more specifically, the squared multiple correlation coefficient between a variable and all other variables (Norusis, 1990). The *eigenvalue* is the total variance explained by each factor. Factor *loadings* are the weights assigned to the independent variables, and indicate the importance that a single variable has in a specific factor.

The number of factors considered during interpretation are based on specific criteria. A numerically viable solution of the iterative algorithms is to have as many factors as variables. If all factors are used, each variable is exactly represented by them; however, this defeats the other stated goal of data reduction. Two methods are suggested (Norusis, 1990) for choosing the number of included factors while still adequately representing the original information. Both methods are based on the amount of variance accounted for by each factor, and the amount of variance accounted for in total. The first method is to simply retain those factors with eigenvalues greater than 1. The second method is graphic evaluation of eigenvalues. Typically, there is a sharp drop in the eigenvalues around 1 to 2,

between the variance accounted for by the larger factors and each succeeding smaller amount of variance.

Due to limited data, subsets of sampled VOCs were selected to obtain a robust factor analysis solution. VOCs were chosen for inclusion using the criterion of potential source strength, as demonstrated by the magnitude of the Indoor/Outdoor (I/O) ratio. Although they did not meet this criteria, trichlorofluoromethane (freon) and ΔCO_2 were also included in the limited subset of compounds used in factor analysis, based on *a priori* knowledge of sources of pollutants likely to be important in this particular data set; trichlorofluoromethane is a good tracer for air-conditioning where the I/O ratio is greater than 1, and ΔCO_2 is a marker of occupant bioeffluent.

Factor analyses were run and the resulting eigenvalues plotted. As can be seen in Figure 6, the first factor accounted for the greatest proportion of the variance (eigenvalue). Between the fifth and sixth factor the eigenvalues drop from 1.2 to 0.78, and rapidly decrease to <0.001; therefore, five factors were retained for interpretation. Table 14 shows the VOCs, factors, loadings, and communalities; factors with loadings greater than the absolute value of 0.4 were considered interpretable.

Overall, 89% of the variance was accounted for by five factors. The first factor contained 43% of the variance in the data, was the strongest and most distinct factor, and was observed repeatedly across analyses. The remaining four factors were less distinct. Interpretation of factor analysis was based on knowledge of sources and specific
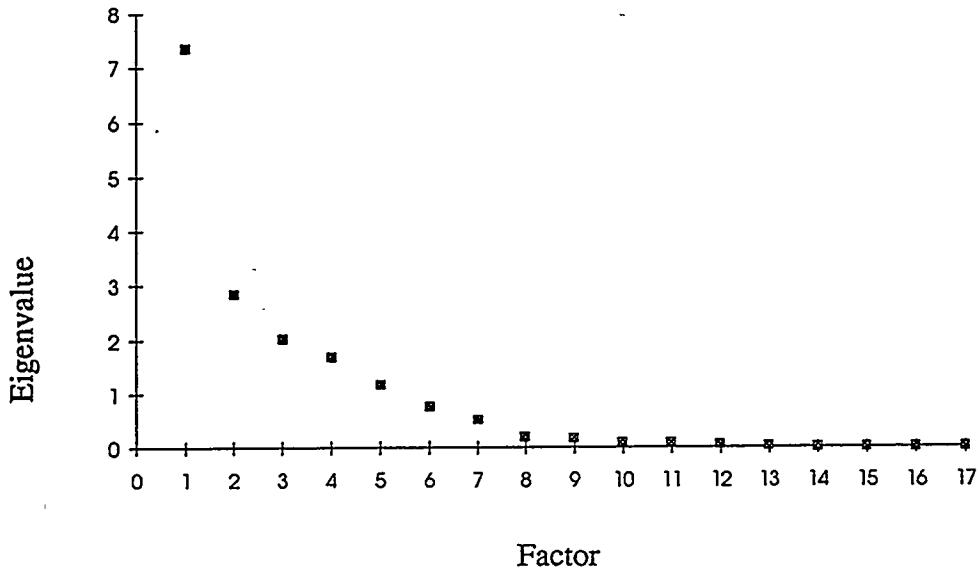
FIGURE 6. Eigenvalues by factors for CHBS VOCs

knowledge of data and site information. All factors were identified and discussed in detail below.

Motor Vehicle Emissions

The factor analyses consistently gave a first factor which had high loadings (typically 0.8 to 0.98) on the aromatic hydrocarbons and a few other VOCs associated with motor vehicle emissions, specifically, those listed for this source in Table 13, plus ethylbenzene, methylcyclopentane, n-hexane and 1,2,3-trimethylbenzene. A motor vehicle emissions factor has been reported previously, with a similar suite of compounds loading highly together on the first factor and accounting for the largest proportion of the variance, although not identified as such by the authors (Noma et al., 1988; Heavner et al., 1995).

TABLE 14. Factor analysis results: Compound loadings for 5 factors (eigenvalue > |.4| underlined)

Compounds	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5	Communality
Benzene	0.845	-0.336	0.02	0.271	-0.033	0.90
m/p-Xylene	0.957	-0.199	0.111	-0.101	-0.025	0.98
o-Xylene	0.965	-0.194	0.092	0.006	-0.015	0.98
1,2,4-Trimethylbenzene	0.959	-0.188	0.14	0.046	-0.061	0.98
1,3,5-Trimethylbenzene	0.734	-0.477	0.363	0.025	0.247	0.96
n-Pentane	0.876	-0.042	-0.292	-0.241	0.14	0.93
n-Pentanal	-0.306	0.849	-0.096	-0.126	0.294	0.93
n-Hexanal	-0.255	0.876	-0.147	0.034	-0.267	0.93
n-Dodecane	-0.216	0.884	-0.118	-0.206	-0.191	0.92
2-Propanone	-0.11	0.802	-0.187	0.400	0.201	0.89
ΔCO_2	-0.287	0.891	-0.127	0.027	0.236	0.95
n-Decane	0.226	-0.186	0.908	0.066	-0.144	0.94
n-Nonane	-0.041	-0.217	0.917	-0.123	-0.028	0.91
Limonene	0.097	0.246	-0.188	0.598	-0.336	0.58
Tetrachloroethylene	-0.084	-0.365	-0.282	0.769	-0.171	0.84
Ethanol	-0.028	0.046	0.346	0.659	0.103	0.57
Trichlorofluoromethane	0.069	0.11	-0.148	-0.135	0.937	0.93
Variance (%)	43	17	12	10	7	Overall 89%
Probable Source Type	Motor Vehicle Emission	Building Materials and Occupants (bioeffluents)	Room Freshener/ Deodorizer	Bioeffluent and Cleaning Products	HVAC-Associated	

Table 15 gives the ratios of the concentrations of these VOCs to benzene for a motor vehicle emissions profile from Chicago (Doskey et al., 1992) and for the outdoor air samples from this study. The ratios for outdoor air and motor vehicle emissions are very similar, although the motor vehicles emissions profile for California would be expected to differ somewhat from the Chicago profile because of differences in the mix of catalyst and non-catalyst vehicles and in fuel composition.

The VOCs reported in the literature to be from motor vehicle emissions matched the observed grouping of VOCs with high loadings on the first factor from factor analysis.

Figure 7 demonstrates that, except for toluene, these ratios are very similar. VOCs from

motor vehicle emissions contribute to concentrations of these compounds; thus the

California outdoor air concentration profile was used as a motor vehicle emissions profile

and the contributions of motor vehicle emissions to indoor VOCs were estimated using the

following approximation for 10 of the 13 buildings[1]:

$$C_{x,i,mv} = \left(\frac{C_x}{C_{bz}}\right)_{mv} \times C_{bz,i} \qquad \text{(EQ 1)}$$

where:

$C_{x,i,mv}$ = concentration of compound x, in indoor air in building i, originating from motor vehicle emissions, mv;

$\left(\dfrac{C_x}{C_{bz}}\right)_{mv}$ = ratio of concentrations of compound x and benzene in motor vehicle emissions;

$C_{bz,i}$ = indoor concentration of benzene in building i.

In this receptor source apportionment approximation (Henry et al., 1984; Morandi et al.,

1987), it was assumed that 100% of indoor benzene was from motor vehicles. The I/O

ratios for benzene in the ten buildings for which the estimation was done were all close to

one. Two of the remaining three spaces were excluded from this calculation because there

was evidence of indoor sources of benzene (the reference compound), i.e., I/O was greater

than 1.35 for benzene in spaces 5.2 and 5.6. The third space was excluded because of the

lack of an outdoor sample for Building 6.

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1. Building 5 and 6 were not used in the analysis, leaving an effective total of 10 buildings. See Table 15, footnote a.
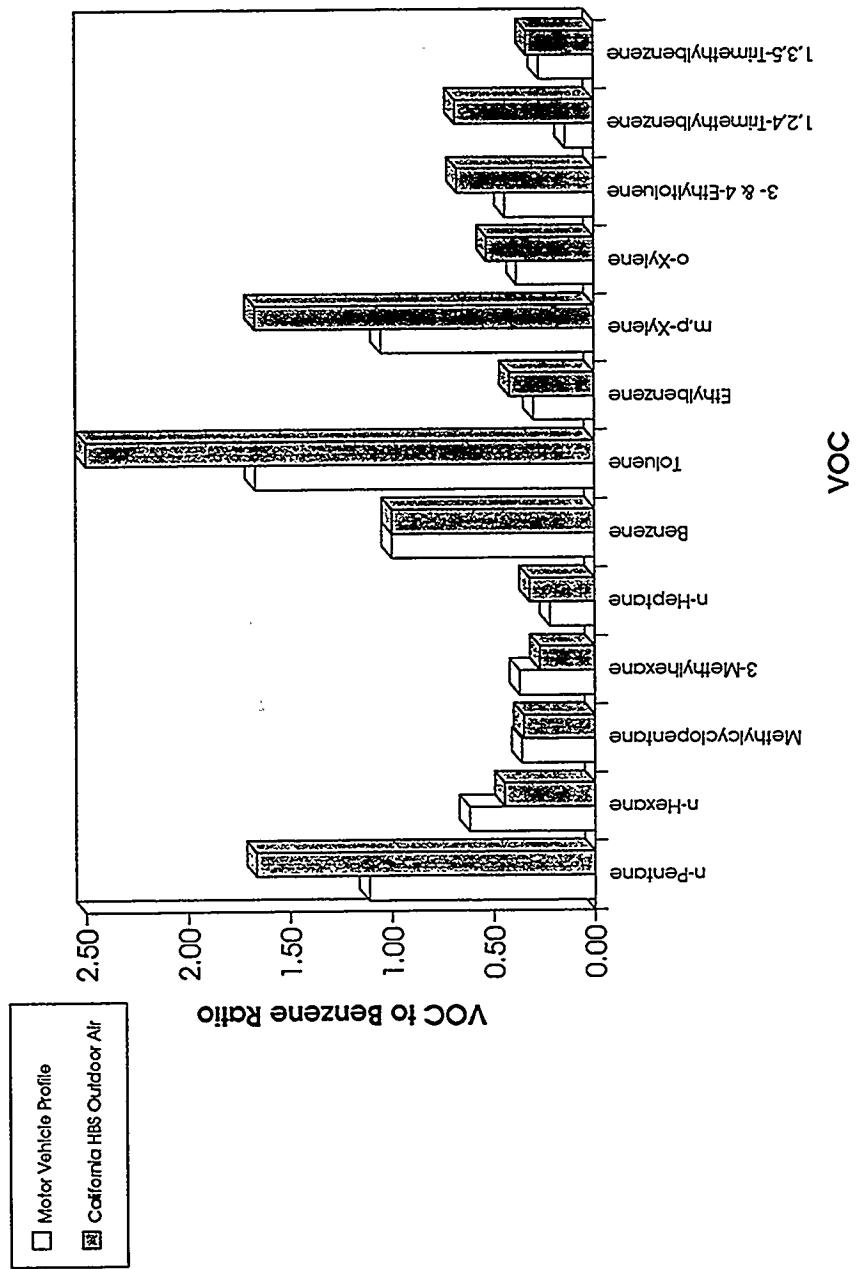
FIGURE 7. Ratios of VOC to benzene (arithmetic mean in ppb, Buildings 5 & 6 excluded): Motor vehicle profile versus outdoor air

The percent of indoor VOC from motor vehicle emissions was calculated for each of ten buildings, and then averaged across the ten buildings. Averages are reported in Table 15.

TABLE 15. Comparison of ratios of selected VOCs to benzene in motor vehicle emissions and in outdoor air samples and estimated contribution of motor vehicle emissions to indoor concentrations for 10/13 of the office buildings[a]

| Compound | Ratios of VOC to Benzene | | Estimated Percent of Indoor Air Concentration from Motor Vehicle Emissions Averaged over Buildings |
	Motor Vehicle[b]	California Outdoor Air[c]	
n-Pentane	1.11	1.66	80
n-Hexane	0.62	0.44	100
Methylcyclopentane	0.36	0.35	71
3-Methylhexane	0.37	0.27	81
n-Heptane	0.22	0.32	71
Benzene	1(Reference)	1(Reference)	100 (Reference)
Toluene	1.67	4.19	86
Ethylbenzene	0.30	0.42	76
m/p-Xylene	1.05	1.37	77
o-Xylene	0.38	0.53	74
3/4-Ethyltoluene	0.44	0.68	76
1,2,4-Trimethylbenzene	0.14	0.69	78
1,3,5-Trimethylbenzene	0.27	0.33	74

a. Buildings 5.2 and 5.6 omitted due to high I/O ratio for benzene; Building 6 omitted due to lack of outdoor sample.

b. Doskey et al., 1992.

c. This study.

These calculations indicate that 71% to 100% (arithmetic mean 79% ± 8.0%, excluding benzene) of these compounds originated from motor vehicle emissions in outdoor air.

Motor Vehicle Emissions VOCs Across Ventilation Types

Figure 2 demonstrates visually that differences among all VOCs exist across ventilation types, but does not show the degree of statistical significance. Compounds from motor vehicle emissions show small but significant differences in levels by ventilation type. Motor vehicle compounds in MV buildings are elevated compared to medians of NV and

AC ventilation types (excluding 3-methylhexane, which is elevated in NV and AC

ventilated buildings, and toluene, which is elevated in AC ventilated buildings).

The Wilcoxon Rank-Sum test (a nonparametric test with no assumptions regarding

distribution) was used to explore differences in motor vehicle emissions across buildings

and ventilation types. The null hypothesis is that the two tested medians are the same; H_0:

there is no difference between the medians. Table 16 presents the arithmetic means ±

TABLE 16. Comparison of average concentrations of motor vehicle emissions compounds in mechanically ventilated buildings versus air conditioned and naturally ventilated buildings: Arithmetic mean ± standard deviation and Wilcoxon Rank-Sum test

Compound	Arithmetic Mean ± Standard Deviation			Wilcoxon Rank-Sum test H_0: difference=0		
	Mechanical Ventilation	Natural Ventilation	Air Conditioning Ventilation	MV=NV p > |t| =	AC=NV p > |t| =	MV=AC p > |t| =
n-Pentane	5.5 ± 3.5	1.8 ± 0.42	3.5 ± 2.1	0.10	0.19	0.20
n-Hexane	1.1 ± 0.55	0.52 ± 0.07	0.69 ± 0.43	0.10	0.27	0.16
Methylcyclopentane	0.79 ± 0.44	0.39 ± 0.17	0.50 ± 0.20	0.20	0.25	0.20
3-Methylhexane	0.51 ± 0.21	3.1 ± 1.1	3.1 ± 1.1	0.12	0.42	0.11
n-Heptane	0.53 ± 0.16	0.40 ± 0.67	0.40 ± 0.13	0.17	0.76	0.13
Benzene	1.8 ± 0.99	1.3 ± 0.66	1.2 ± 0.67	0.27	0.84	0.13
Toluene	3.5 ± 1.8	2.5 ± 1.1	4.1 ± 4.2	0.20	0.16	0.46
Ethylbenzene	0.72 ± 0.23	0.41 ± 0.15	0.55 ± 0.17	0.04	0.06	0.20
m/p-Xylene	3.4 ± 1.2	1.7 ± 0.61	2.3 ± 0.99	0.04	0.23	0.06
o-Xylene	1.1 ± 0.37	0.56 ± 0.22	0.71 ± 0.28	0.04	0.31	0.10
3/4-Ethyltoluene	1.2 ± 0.57	0.61 ± 0.18	0.85 ± 0.37	0.17	0.27	0.21
1,2,4-Trimethylbenzene	1.2 ± 0.64	0.69 ± 0.24	0.85 ± 0.40	0.20	0.34	0.20
1,3,5-Trimethylbenzene	0.55 ± 0.15	0.36 ± 0.08	0.40 ± 0.19	0.04	0.23	0.20
1,2,3-Trimethylbenzene	0.8 ± 0.32	0.10 ± 0.12	0.49 ± 0.23	0.01	0.004	0.09
2-Ethyltoluene	0.72 ± 0.28	0.55 ± 0.21	0.42 ± 0.20	0.10	0.19	0.03

standard deviations of these compounds, and the results of the test. Below 10% (p > 0.10)

for eight out of fifteen of this suite of compounds we can reject the null hypothesis that the

medians of the motor vehicle emissions VOCs from the MV and NV buildings are equal.

The compounds in the MV buildings are elevated above the same compounds in the NV buildings. The three MV buildings are all located very close to major highways; this proximity is suspected to be the reason for the somewhat higher concentrations of these motor vehicle-associated compounds in the MV buildings. By comparison, the overall results of the Wilcoxon Rank-Sum test of differences in motor vehicle emissions do not indicate that the null hypothesis of similarities between MV and AC, or AC and NV, ventilation types can be rejected.

Other Sources of VOCs

Factor 2 loads strongly on a suite of highly correlated compounds associated with building materials and building occupants. I/O ratios indicate that indoor sources dominate for all five compounds. Building materials are a probable source of the first three compounds, n-pentanal (0.85) (Molhave, 1982; Berglund et al., 1989), n-hexanal (0.88) (Wolkoff et al., 1990), and n-dodecane (0.88) (Molhave, 1982). Two known bioeffluents, ΔCO_2 (0.89) and 2-propanone (0.80), are strongly associated together on the same factor. The ΔCO_2 is a commonly used indicator of occupant- adjusted ventilation, and CO_2 is emitted in relatively large quantities by humans (Wang, 1975). CO_2 was found to be the most abundant inorganic bioeffluent measured in a college classroom (Wang, 1975). Wang (1975) has found 2-propanone to be one of the elevated organic compounds in bioeffluents. The ratio of CO_2 to 2-propanone emission factors from Wang (1975)

($\dfrac{CO_2}{2-propanone} = 12 \times 10^3$) is in close agreement with the ΔCO_2 to 2-propanone ratio

calculated from values of the current study ($\frac{\Delta CO_2}{2-propanone} = 19 \times 10^3$), and supports the

identification of 2-propanone on this factor as a bioeffluent. The association of 2-propanone and ΔCO_2 with three building material compounds reflects the association of the bioeffluent source with the buildings, i.e., building occupants and buildings.

Two compounds, *n*-decane (0.89) and *n*-nonane (0.91), load highly on the third factor, which has been identified as a room freshener/deodorizer source. Possible sources for *n*-decane include deodorizers (room fresheners) (Tichenor, 1989), motor vehicles (Noma et al., 1988; Doskey et al., 1992), building materials (Molhave, 1982), solvents (Lebret et al., 1986), and paint remover (solvent) (Wallace et al., 1989). Possible sources for *n*-nonane include deodorizers (Tichenor, 1989), motor vehicles (Noma et al., 1988), building materials (Miksch et al., 1982; Molhave, 1982), and solvents (Lebret et al., 1986). Deodorizers and air fresheners commonly used for odor masking often contain *n*-decane and *n*-nonane, as well as a typical marker compound for deodorizers, 1,4-dichlorobenzene (Levin, 1989). Headspace analysis (using GC-MS to identify compounds) identified *n*-nonane and *n*-decane (and others) as major organic compounds in room fresheners (Tichenor, 1989). As *n*-nonane and *n*-decane are major VOC components emitted by deodorizers, this factor has been identified as being associated with air fresheners. In a recent study (Heavner et al., 1995) on VOCs in smoking and non-smoking homes, these three marker compounds were reported together on the same factor. In the study, *n*-nonane (0.68), *n*-decane (0.91), and 1,4-dichlorobenzene (0.80) were found to be highly loaded

and grouped together on a separated factor from the other 28 VOCs, although the factor was not identified by the authors.

Although *n*-decane and *n*-nonane in the current study have been identified as originating predominantly from outdoor air based on their I/O ratios (see Table 13), indoor sources dominate concentrations in three buildings. The I/O ratios for both compounds in the same three buildings are greater than 2. The influence of the three buildings dominated by indoor sources of these 2 VOCs on the factor analysis results was tested using factor analysis with and without the buildings. Elimination of the buildings with indoor sources of *n*-decane and *n*-nonane replicates the loadings and the compound groupings of all factors presented in Table 14 *excepting* Factor 3, indicating that the three buildings with indoor sources of these compounds drive this factor.

Tetrachloroethylene (0.77), ethanol (0.66), limonene (0.60), and 2-propanone (0.40), are the most highly loaded VOCs on Factor 4. This factor has been identified as a combined "bioeffluent and cleaning products" source. Identification of the factor is based on the observed I/O ratios and reported associations of various compounds in indoor and ambient air. Dry cleaning is the major source of tetrachloroethylene in both indoor and outdoor urban air. Ambient air levels of tetrachloroethene are almost entirely from dry cleaning sources (Scheff et al., 1989). Indoor concentrations of tetrachloroethene are due largely to infiltration from ambient air, plus contributions from indoor sources. Indoor sources include dry cleaned clothing (Wallace, 1989), exhaled breath (Wallace et al., 1985), and cleaning products (Wallace et al., 1986). The I/O ratios for the buildings in this study

suggest that outdoor air is the major source of tetrachloroethene, for 8 of the 12 buildings that had I/O ratios that were less than or equal to 1.35. In the remaining four buildings, the I/O ratio was 1.35 to 3, indicating that in these buildings there were also contributions from indoor sources.

Limonene is a compound often used in cleaners and solvents (Lebret et al., 1986; Wallace, 1986) for its masking, citrus odor. Tetrachloroethylene is also used as a solvent and for degreasing of metals (Windholz, 1983; Scheff et al., 1989). High loadings of limonene (0.60) and tetrachloroethylene (0.77) on the same factor have been reported in a previous factor analysis on compounds observed in sick and healthy buildings in Sweden (Noma et al., 1988)[1]. In the current study, 10 out of 12 buildings had I/O ratios for limonene greater than 1.35. For 3 buildings the I/O ratio was greater than 10, while for 1 building the I/O ratio was greater than 20. These large I/O ratios strongly support indoor sources of origin for limonene. On this factor, tetrachloroethylene and limonene are positively associated with ethanol and 2-propanone, which are likely to be bioeffluents. As noted before, the ratios of the concentrations of ΔCO_2 to 2-propanone for these buildings are very similar to the ratio of emission factors for CO_2 and 2-propanone in human bioeffluents (Wang, 1975). Similarly, the ratios of ΔCO_2 to ethanol observed in this study ($\frac{\Delta CO_2}{ethanol} = 4 \times 10^3$) are within good agreement with the CO_2 to ethanol emission factor ratios ($\frac{CO_2}{ethanol} = 11 \times 10^3$) (Wang, 1975).

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1. Limonene (0.66) and tetrachloroethylene (0.58) loaded highly together on Factor 3 in Table 8.

Factor 5 had a very high loading for trichlorofluoromethane (freon) (> 0.94), and the factor has been identified as a heating, ventilation and air conditioning systems-associated (HVAC-associated) source. The distribution of reported outdoor values of trichlorofluoromethane (median 0.20 ppb, lower and upper quartile values of 0.19 and 0.21 ppb, based on 1507 data points) (Shah and Singh, 1988) and the indoor concentrations reported herein (geometric indoor mean of 0.89 ppb and geometric outdoor mean of 0.43 ppb) overlap. For 5 of the buildings, the indoor and outdoor concentrations of the trichlorofluoromethane were very similar (i.e., the ratio was close to 1). For 4 of the 7 AC buildings, 2 of the MV buildings, and 1 NV building, the I/O ratio of this compound was greater than 1.9 and reached as high as 17. This compound is commonly used as a refrigerant and is probably leaking from the HVAC systems or from some refrigeration system in these buildings. The MV and NV buildings which had excess trichlorofluoromethane are all physically connected to AC buildings. Therefore, this factor has been identified as an "HVAC-associated" source.

In summary, the factor analysis has identified two strongly represented sources. A motor vehicle emissions source is observed repeatedly on the first factor. A bioeffluents, building occupants source is split between two separate factors. These two sources are repeatedly represented in the current and often seen in previous factor analyses on buildings. Based on the strength and consistency of these associations, as well as the ubiquitousness of the sources, future factor analysis of other buildings may be expected to find these two

factors. However, the other factors identified herein may be unique to this suite of compounds and buildings.

Descriptive Statistics: Subjects

Self-administered questionnaires[1] were returned by CHBS participants (n=880, 85% response rate) with information on personal, psychological, job and workspace factors, as well as SBS symptoms[2]. The questionnaire used is briefly described in the following quotation from Mendell (1991):

> "The questionnaire asked about the frequency of 15 symptoms occurring at work, during the previous week and also during the previous year, and whether each symptom changed when the respondent was not at work."

Symptoms were considered "building related" if they were reported as being experienced within the building, but improving on days not in the building. Binary symptom outcomes (yes/no) were based on whether individuals experienced "building related" symptoms three or more days "last week", where questionnaire administration was timed so that "last week" would be the week of microenvironmental sampling.

As per the discussion in "VOC and Subject Database", a subset of the original responses was used for this investigation. Available VOC samples were judged to be inadequate to represent exposures of 137 individuals out of the total. In addition, 226 individuals did not

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1. In Appendix A, full text of questionnaire has been reprinted with permission (Mendell, 1991).
2. The major conclusions based on the full CHBS data set are reported elsewhere (Mendell, 1991; Fisk et al., 1993). Note that the results reported herein are from a subset of the original data, and therefore differ slightly.

complete questionnaires at the appropriate time. The final joint database contained 517 individuals located in 12 buildings.

Demographic Information for Subjects

Demographic information on individuals in the subset of data used in this study (n=517) is presented in Table 17. Most of the individuals are located within areas of low or medium TVOC values (TVOC less than 2000 ug m^{-3}). Gender distribution is slightly skewed; two thirds of the subjects are female (68%), while one third of the subjects are male (32%). Two thirds of the study subjects (62%) are in air conditioned buildings, while 25% of the subjects are in mechanically ventilated buildings and 13% in naturally ventilated buildings (13%). A majority of subjects (66%) are above 50 years of age. Almost half of the subjects are Caucasian (49%), with the remaining subjects spread across African American, Asian - Pacific Islander and Hispanic ethnic groups. Subjects are also distributed across education and job categories.

Symptoms

Variables used to approximate the suite of symptoms reported in cases of "sick building syndrome" are defined in Table 18. These include individual symptoms of sensory irritation (dry, irritated or itching eyes; dry or itchy skin; dry or irritated throat), deep pulmonary stress (chest tightness, difficulty breathing), and neurogenic irritation (headache, sleepiness, fatigue). Subjects were also queried regarding three symptoms

65

TABLE 17. Demographic information on individuals within low/medium and high TVOC exposure categories

Demographic Information[a]	Low/Medium TVOC tvoc < 2000 μg m^{-3} (n = 455) %	High TVOC tvoc > 2000 μg m^{-3} (n = 62) %	Totals (n = 517) %
Gender			
male	93	7	32
female	86	14	68
Smoking status			
never	91	9	51
ever	84	16	49
Sensitive population[b]			
normal	88	12	46
sensitive	88	12	54
Job category			
managerial	87	13	21
professional	91	9	16
technical	79	21	7
clerical	85	15	41
case worker	100	0	14
other	83	17	2
Ventilation type			
natural	100	0	13
air conditioning	82	18	62
mechanical	96	4	25
Age (years)			
<=29	50	50	0.4
30-39	86	14	10
40-49	93	8	23
50+	87	13	66
Ethnicity			
Caucasian	80	20	49
African American	97	3	15
Asian - Pacific Islander	100	0	22
Hispanic	82	18	10
other	100	0	5
Education			
<=11th Grade	100	0	0.4
High School Graduate	79	21	23
2 Years of Graduate Education	88	12	19
Bachelor Degree	97	3	25
Some Graduate Education	92	8	13
Graduate/Professional	84	16	20

a. Denominators will differ depending upon missing (unreported) information.

b. Defined in this study as individuals having either doctor-diagnosed asthma, or self-diagnosed hay fever.

TABLE 18. Definition of symptoms (individual and composite)

Symptoms	Building related symptoms occurring three or more times during week of sampling
Individual	
eye	dry, irritated, or itching eyes
skin	dry or itchy skin
throat	dry or irritated throat
chest	chest tightness
difficulty breathing	difficulty breathing
runny nose	runny nose
stuffy nose	stuffy nose
sleep	sleepiness
fatigue	fatigue
headache	headache
ear	earache
shoulder	shoulder pain or numbness
tooth	toothache
Composite	
irritant	reporting at least one of the following: eyes, skin, throat
irritated mucous membrane	reporting at least one of the following: runny nose, stuffy nose, throat, eyes
overall	reporting at least one of the following: chest, difficulty breathing, runny nose, stuffy nose, sleep, fatigue, headache

believed not to be part of the SBS syndrome (earache, shoulder pain or numbness, toothache), to obtain some indication of symptom over-reporting.

Composite variables were developed based on at least one positive report of any of the individual symptoms. Irritant variables were composed of sensory irritation symptoms (dry, irritated or itching eyes; dry or itchy skin; dry or irritated throat). The irritated mucus membrane variable is composed of reports of symptoms of runny nose, stuffy nose, throat irritation, or eye irritation. The overall variable is composed of general systemic symptoms (tight chest, difficulty breathing, runny nose, stuffy nose, sleepiness, fatigue, headache).

Symptom prevalence is the number of individuals reporting they experienced a symptom, divided by the total number of individuals responding to the question multiplied by 100%.

Symptom prevalences across all study buildings are shown in Figure 8. One of the buildings eligible for this study is a complaint building, with a known history of occupant complaints. Prevalences are significantly impacted by the complaint building. For this reason, analyses were adjusted by presence of the complaint building by inclusion of an indicator variable for complaint building status.

Overall, prevalences were highest for individual symptoms of fatigue (29%), sleepiness (28%), and dry, irritated or itching eyes (23%). Individuals reported non-SBS symptoms of earache and toothache at 2% and 1% respectively; 13% overall reported shoulder pain or numbness. Without the complaint building, prevalences are somewhat lower: fatigue (23%), sleepiness (22%), and dry, irritated or itching eyes (17%). By comparison with overall prevalence and prevalence without the complaint building, symptom prevalences in the complaint building alone are quite elevated: fatigue (54%), sleepiness (50%), and dry, irritated or itching eyes (43%).

Table 19 gives totals for all symptom responses (yes and no). Over one thousand responses were reported in the complaint building. The extent of response, seen in both Table 19 and Figure 8, is an example of a system that has been perturbed, where subjects are aware of the issue due to the history of the building. The elevated symptom prevalence in the buildings may be caused by over-reporting prompted by this awareness, or may be due to single or multiple causal factor(s), or there may not be any reporting bias (i.e., no over-reporting). Distinguishing between the causes of elevated symptom reporting is a
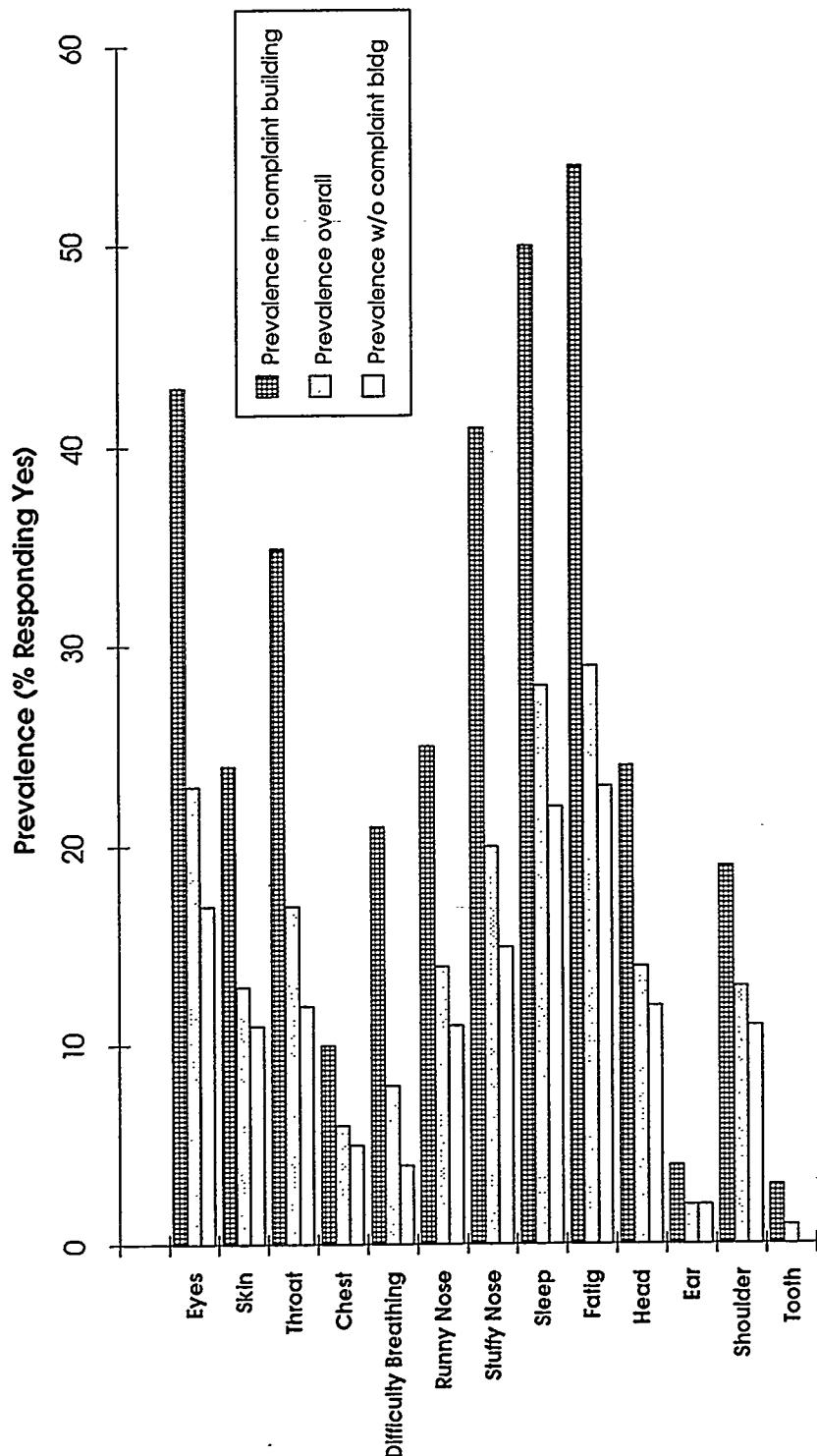
FIGURE 8. Prevalence of symptoms: Prevalence overall, Prevalence without complaint building, prevalence in complaint building

TABLE 19. Number of subjects reporting symptoms (Yes and No) by building

Bldg. #	Eyes		Skin		Throat		Chest		Difficulty Breathing		Runny Nose		Stuffy Nose		Sleep		Fatigue		Headache		Ear		Shoulder		Tooth		Totals	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	3	12	2	12	4	9	3	11	2	13	2	12	3	11	3	12	5	10	4	11	1	13	4	11	1	1	37	151
2	43	57	23	72	34	63	9	83	19	73	24	71	39	55	48	48	52	45	23	71	4	92	17	71	3	3	338	895
3	3	21	2	22	4	21	1	24	0	25	1	24	2	23	3	21	5	19	2	22	0	25	2	21	0	0	25	293
4	8	32	3	36	5	34	1	40	0	42	3	35	4	34	6	31	10	27	5	36	0	40	6	31	0	0	51	459
5.2	0	11	1	10	0	11	0	11	1	10	1	10	0	10	1	10	1	10	0	11	0	11	2	9	0	0	7	135
5.6	0	15	0	15	1	13	1	14	0	15	0	15	0	14	0	15	1	14	1	14	0	15	3	12	0	0	7	186
6	5	31	4	31	4	31	1	36	1	36	7	29	6	30	8	29	7	30	3	34	0	35	1	34	0	0	47	424
7	12	45	12	47	7	54	4	56	4	55	8	51	12	48	18	41	13	47	7	52	2	61	7	54	0	0	106	474
8	11	43	4	47	7	44	3	52	3	52	7	48	10	43	13	40	12	40	4	49	2	52	9	45	0	0	85	610
9	2	22	2	21	1	21	0	25	0	23	0	25	3	21	4	19	6	16	2	19	0	25	0	22	0	0	20	284
10	1	17	1	15	2	15	1	18	2	16	1	16	2	14	3	13	1	16	3	15	0	18	0	17	0	0	17	209
11	17	40	8	50	8	48	4	52	4	52	9	48	8	47	20	36	20	37	9	46	2	55	6	48	0	0	115	613
12	3	24	1	27	1	27	0	33	0	30	1	26	6	21	5	23	6	26	4	27	0	28	2	27	0	0	29	352
Totals	108	370	63	405	78	391	28	455	36	442	64	410	95	371	132	338	139	337	67	407	11	470	59	402	4	4	884	5285

complex research issue; potential cause(s) of the observed elevated symptom prevalences

will be discussed in the following chapters.

Appendix

Appendix A The California Health Building Study Questionnaire
(Mendell, 1991)

THE HEALTHY BUILDING STUDY
CONSENT FORM
(Return this form to us with the questionnaire!)

This study will tell your employer and building manager about worker experience in your office environment (though neither they nor anyone else at work will know your <u>individual</u> answers on the questionnaire).

All questionnaires will be kept locked up, and then destroyed after data analysis is complete. Results of the study will be provided in a report to you and other employees, to employee representatives, and to your employer; results will contain <u>group data only</u>, without any personal identifiers.

<u>I WOULD LIKE TO PARTICIPATE</u> IN THE HEALTHY BUILDING STUDY:

I have read the previous instructions for the "Healthy Building Study", and consent to participate.

_____   _____   _____
name (please print)   participant's signature   date

We will distribute to you a report of the study results when they are available.

NEXT, PLEASE TURN TO THE BACK OF THIS PAGE.

<u>I DO NOT WANT TO PARTICIPATE</u> IN THE HEALTHY BUILDING STUDY:

_____   _____
name (please print)   date

reason (optional): _____

_____

If you choose not to participate, please fold the <u>blank</u> questionnaire,
seal it in the envelope provided,
and return it to the box marked "Building Study", located near your mailbox.

PLEASE READ BEFORE COMPLETING QUESTIONNAIRE

Many questions in this questionnaire mention either "LAST WEEK" or "LAST YEAR".

LAST YEAR refers to <u>the 12-month period ending today</u>. If you have worked in this building for less than one year, answer the "LAST YEAR" questions for that part of the year that you have worked in this building.

LAST WEEK refers to <u>all days you worked from Monday through Friday of last week</u> (not this week). Please report your ACTUAL EXPERIENCES LAST WEEK, even if last week was unusual for you. If you were not at work all of last week, answer for the most recent full week you were in the office.

Please fill out this questionnaire without discussing it or consulting about it with others: we want your own immediate opinions and responses.

We would like you to answer all the questions as completely as possible, but you do not have to answer any questions that you do not want to, and you may stop at any time.

_____

PART I. DESCRIPTION OF YOUR WORKSTATION

This section asks you about your workstation. By WORKSTATION we mean your desk, office, cubicle, or place that is your primary work area. If you work in more than one location, your workstation is the specific location where you spend more time than at any other single location.

1. There are many different types of workstations. Please check the categories that best describe the space in which your current workstation is located.

   a. Type of space (Check one)

      1. ☐ Enclosed office with door

      2. ☐ Not an enclosed office, but with partitions or bookshelves giving you visual privacy on four sides

      3. ☐ Not an enclosed office, but with partitions or bookshelves giving you visual privacy on one, two, or three sides

      4. ☐ Open office area, with no visual privacy

      5. ☐ Other (specify) _____

      _____

   b. Type of space sharing (Check one)

      1. ☐ One occupant only

      2. ☐ Shared with one other person

      3. ☐ Shared with two or more other persons

      4. ☐ Other (describe) _____

      _____

2. On what floor of the building do you work? (Enter the floor number; if the basement, write B.)

   ☐☐ floor

3. How long have you been working in the building? (If less than one year, enter number of months)

   ☐☐ years (☐☐ months)

4. a. How long have you worked at your current workstation? (If less than one year, enter number of months)

   ☐☐ years (☐☐ months)

   b. During an average workday, how many hours do you spend at your workstation?

   ☐☐ hours per day

5. a. During a typical week, how many hours do you work in the building?

   ☐☐ hours per WEEK

   b. LAST WEEK, how many hours did you work in the building?

   ☐☐ hours LAST WEEK

6. LAST WEEK during a typical day, approximately how much time did you spend working with each of the following items? (*If less than 1 hour per day, enter minutes.*)

		hours per day	(minutes per day)
a.	Computer or word processor with screen/keyboard	☐☐	☐☐
b.	Photocopy machine .	☐☐	☐☐
c.	Carbonless copies (NCR paper)	☐☐	☐☐

NOTE:
For the following questions, think of the area within a circle of about 15 feet from your workstation in all directions.

7. Are any of the following items now located within 15 feet of your current workstation? (*Check "no" or "yes" for each item.*)

		No 1	Yes 2
a.	Photocopy machine	☐	☐
b.	Laser printer....................	☐	☐
c.	Plants	☐	☐
d.	Window	☐	☐

(If No on "d" go to Q. 9)

8. . Is there ever a window open within 15 feet of your desk?

1. ☐ No

2. ☐ Yes

9. During the LAST YEAR (or since you've been at your current workstation, if that is less than a year) have any of the following changes taken place within 15 feet of your current workstation? (*Check "no" or "yes" for each item.*)

		No 1	Yes 2
a.	New carpeting	☐	☐
b.	New plants	☐	☐
c.	Walls painted	☐	☐
d	Walls rearranged or moved	☐	☐

PART II.
INFORMATION ABOUT YOUR HEALTH AND WELL-BEING

1. *Please answer the three questions to the right (A, B, C) about each symptom listed below*

A. How often during the LAST YEAR* did you experience this symptom while working in the building?

(If "never", skip questions B and C and go down to the next symptom.)

	never 1	rarely 2	some-times 3	often 4	always 5

B. How many days LAST WEEK** did you experience this symptom while working in the building?

(Fill in # of days LAST WEEK)

C. Does the symptom usually change when not at work?

	gets worse 1	stays same 2	gets better 3

Symptom	A. never 1	rarely 2	some-times 3	often 4	always 5	B. # days	C. gets worse 1	stays same 2	gets better 3
a. runny nose	☐	☐	☐	☐	☐	☐	☐	☐	☐
b. stuffy nose/sinus congestion	☐	☐	☐	☐	☐	☐	☐	☐	☐
c. dry or irritated throat	☐	☐	☐	☐	☐	☐	☐	☐	☐
d. earache	☐	☐	☐	☐	☐	☐	☐	☐	☐
e. dry or itchy skin	☐	☐	☐	☐	☐	☐	☐	☐	☐
f. dry, irritated, or itching eyes	☐	☐	☐	☐	☐	☐	☐	☐	☐
g. problems with contact lenses	☐	☐	☐	☐	☐	☐	☐	☐	☐

continue on next page

*LAST YEAR *refers to the 12 month period ending today (or for the time you've worked in the building if less than one year).*
**LAST WEEK *refers to any or all days worked from Monday through Friday of last week.*

PART II, CONTINUED

1. Please answer the three questions to the right (A, B, C) about each symptom listed below

A. How often during the LAST YEAR* did you experience this symptom while working in the building?

(If "never", skip questions B and C and go down to the next symptom.)

B. How many days LAST WEEK** did you experience this symptom while working in the building?

(Fill in # of days LAST WEEK)

C. Does the symptom usually change when not at work?

	A. never (1)	rarely (2)	some-times (3)	often (4)	always (5)	B. (# days)	C. gets worse (1)	stays same (2)	gets better (3)
h. unusual fatigue or tiredness	☐	☐	☐	☐	☐	☐	☐	☐	☐
i. sleepiness	☐	☐	☐	☐	☐	☐	☐	☐	☐
j. headache	☐	☐	☐	☐	☐	☐	☐	☐	☐
k. chills or fever	☐	☐	☐	☐	☐	☐	☐	☐	☐
l. chest tightness	☐	☐	☐	☐	☐	☐	☐	☐	☐
m. difficulty breathing	☐	☐	☐	☐	☐	☐	☐	☐	☐
n. toothache	☐	☐	☐	☐	☐	☐	☐	☐	☐
o. pain or numbness in shoulder/neck	☐	☐	☐	☐	☐	☐	☐	☐	☐

please go to next question →

LAST YEAR refers to the 12 month period ending today (or for the time you've worked in the building if less than one year).
**LAST WEEK refers to any or all days worked from Monday through Friday of last week.*

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2. a. Today, do you have either a cold, an infection in your lungs or chest, or flu?

    1. ☐ No

    2. ☐ Yes

  b. How many separate times in the LAST YEAR have you had either a cold, an infection in your lungs or chest, or flu? *(Write 0 if none.)*

    ☐☐ times in the LAST YEAR

  c. How many times in the LAST YEAR have you seen a physician because you had either a cold, an infection in your lungs or chest, or flu?

    ☐☐ times in the LAST YEAR

  d. On how many days in the LAST YEAR has either a cold, an infection in your lungs or chest, or flu caused you to stay home from work?

    ☐☐ days in the LAST YEAR

3. During the LAST YEAR, have you had an illness in which you had repeated episodes of three or more of the following symptoms at the same time: wheezing, cough, shortness of breath, fever, chills, aching joints/muscles?

    1. ☐ No

    2. ☐ Yes

4. During the LAST YEAR, have you had any episodes of wheezing (whistling in the chest) without fever or chills or sore throat?

    1. ☐ No

    2. ☐ Yes

5. a. Has a physician ever told you that you have, or had, asthma?

    1. ☐ No ———→ (go to Question 6)

    2. ☐ Yes

  b. If yes, when was it first diagnosed?

    19 ☐☐

  c. Have you had an asthma attack during the LAST YEAR?

    1. ☐ No

    2. ☐ Yes

6. Do you believe you are or may be allergic to any of the following? (Check "no" or "yes" for each item.)

		No 1	Yes 2
a.	pollen or plants	☐	☐
b.	animals	☐	☐
c.	dust	☐	☐
d.	molds	☐	☐
e.	other (specify)	☐	☐

_____

7. Do you wear contact lenses at work?

    1. ☐ Never

    2. ☐ Sometimes

    3. ☐ Often

    4. ☐ Always

PART III.
INFORMATION ABOUT YOUR PRESENT WORK ENVIRONMENT

In this question, you are asked to report specific responses to the physical environment at your present workstation.

1. At your present workstation, HOW OFTEN...

A. ...during the LAST YEAR (Please check one box.)

(If "never", skip question B and go down to next line.)

B. ...during the LAST WEEK (Please check one box.)

	A. during the LAST YEAR					B. during the LAST WEEK				
	never (1)	rarely (2)	some-times (3)	often (4)	always (5)	never (1)	once or twice in the week (2)	3 to 4 times in the week (3)	about once a day (4)	more than once a day (5)
a. was there too much air movement?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
b. was there too little air movement?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
c. did you want to adjust the air movement?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
d. was the temperature too hot?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
e. was the temperature too cold?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
f. did you want to adjust the temperature?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

*LAST YEAR refers to the 12 month period ending today (or for the time you've worked in the building if less than one year).

**LAST WEEK refers to any or all days worked from Monday through Friday of last week.

PART III, CONTINUED

1. At your present workstation, HOW OFTEN...

	A. ...during the LAST YEAR *(Please check one box.)* (If "never", skip question B and go down to next line.)					B. ...during the LAST WEEK *(Please check one box.)*				
	never (1)	rarely (2)	some-times (3)	often (4)	always (5)	never (1)	once or twice in the week (2)	3 to 4 times in the week (3)	about once a day (4)	more than once a day (5)
g. was it too humid?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
h. was it too dry?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
i. did you want to adjust the humidity?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
j. was the air too stuffy?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
k. did you notice unpleasant odors?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
l. were you bothered by noise?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
m. were you bothered by dust or soot?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

*LAST YEAR refers to the 12 month period ending today (or for the time you've worked in the building if less than one year).
**LAST WEEK refers to any or all days worked from Monday through Friday of last week.

2. What kind of lighting do you generally use at your desk or workstation?
(Check no or yes for each item.)

		No 1	Yes 2
a.	fluorescent lights	☐	☐
b.	ordinary light bulbs	☐	☐
c.	natural light	☐	☐
d.	other (specify)	☐	☐

_____

3. Please rate the lighting at your workstation.

1. ☐ Much too dim
2. ☐ A little too dim
3. ☐ Just right
4. ☐ A little too bright
5. ☐ Much too bright

4. Can you see out an outside window from your workstation?

1. ☐ No
2. ☐ Yes

5. How much natural daylight do you have at your usual desk or workstation? (Check appropriate box.)

1. ☐ No natural daylight
2. ☐ Very little natural daylight
3. ☐ A moderate amount of natural daylight
4. ☐ Much natural daylight

6. Are you worried or concerned about the indoor air where you work? (Check appropriate box.)

1. ☐ not at all worried--> (go to Q. 8)
2. ☐ slightly worried
3. ☐ somewhat worried
4. ☐ very worried

7. If you are worried or concerned about the ventilation or indoor air where you work, why is this? (Check no or yes for each item.)

		No 1	Yes 2
a.	because of some personal comfort problems	☐	☐
b.	because of some personal health problems	☐	☐
c	because of health problems of someone else in the building	☐	☐
d.	because of things you have heard or read about certain kinds of buildings	☐	☐
d.	other (specify)	☐	☐

_____

_____

8. Compared to other office buildings, how would you rate the indoor air quality in your building? (Check appropriate box.)

1. ☐ much better than others
2. ☐ somewhat better than others
3. ☐ about the same, or not sure
4. ☐ somewhat worse than others
5. ☐ much worse than others

9. How **satisfied** are you with the following? (Check one box for each item, a through d.)

	Very Satisfied	Mostly Satisfied	Uncertain	Mostly Dissatisfied	Very Dissatisfied
a. control over the lighting at your workstation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. control over the temperature at your workstation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. control over the air movement at your workstation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. the overall physical environment at your workstation (that is, the air quality, temperature, light, noise, odor, etc.) during the LAST WEEK	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e. the overall physical environment at your workstation (that is, the air quality, temperature, light, noise, odor, etc.) during the LAST YEAR	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

PART IV. CHARACTERISTICS OF YOUR JOB

1. Please say how much you agree or disagree with each of the following statements about your job:

	Strongly Agree	Mostly Agree	Uncertain	Mostly Disagree	Strongly Disagree
a. My job is usually interesting	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. I'm happy in my job	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. I dislike my job	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. I am satisfied with my job	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e. I'm enthusiastic about my job	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
f. My job is rather monotonous	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
g. My job is not very stressful	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
h. I usually have to work fast	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
i. I often feel stressed at work	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
j. My job demands a lot of concentration	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
k. I often feel overworked	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
l. I have a lot of control over how my work is done	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
m. I have enough space in my work area to do my work	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
n. Air quality in the office has caused health problems for me	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
o. My workspace gives me adequate visual privacy	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

PART V. CONCLUDING QUESTIONS

This section concludes this survey. Your answers to these questions, like your answers to the previous questions, will be kept confidential. This information is needed for statistical purposes.

1. Are you :

   1. ☐ Male

   2. ☐ Female

2. What was your age on your last birthday? (Check appropriate box.)

   1. ☐ less than 20

   2. ☐ 20 - 29

   3. ☐ 30 - 39

   4. ☐ 40 - 49

   5. ☐ 50 - 59

   6. ☐ 60 or over

3. a. What is your race/ethnic group? (Check the appropriate box.)

   1. ☐ White

   2. ☐ Black

   3. ☐ Asian/Pacific Islander

   4. ☐ Other (specify) _____

   5. ☐ Decline to state

   b. Are you of Spanish/Hispanic origin?

   1. ☐ No

   2. ☐ Yes

   3. ☐ Decline to state

4. Which of the following best describes your job duties and responsibilities? (If more than one applies, check the ONE box for the job duties on which you spend the most time.)

   1. ☐ Managerial (such as administrator, manager, etc.)

   2. ☐ Professional (such as engineer, scientist, lawyer, etc.)

   3. ☐ Technical (such as technician, programmer, etc.)

   4. ☐ Administrative Support (such as clerical, secretarial, word processing, key entry, etc.)

   5. ☐ Other (specify)

   _____

5. What is the highest grade you completed in school?

   1. ☐ 11th grade or less

   2. ☐ High school graduate

   3. ☐ 2 years of college or Associate Degree

   4. ☐ Bachelor's or technical degree

   5. ☐ Some graduate work

   6. ☐ Graduate or professional degree

6. a. Which of the following best describes your history of smoking tobacco products such as cigarettes, cigars, or pipes?

    1. ☐ Never smoked--> (go to Q. 7) .

    2. ☐ Former smoker

    3. ☐ Current smoker

    b. In a typical 24 hour day, how many CIGARETTES do you usually smoke?

    1. ☐ None

    2. ☐ 1 to 5

    3. ☐ 6 to 10

    4. ☐ 10 to 20

    5. ☐ 21 or more

7. Give the date when you finished this questionnaire:

    ☐☐   ☐☐ . 1990
    (month) (date)

10. Is there anything else you would like to tell us about environmental or health matters in your building? If so, please use this space provided for that purpose:

_____

_____

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When you are finished, please:
   fold this questionnaire in half, with the signed consent form,
   seal it in the envelope provided, and
   return it to the place or person described on the front Instruction Sheet.

THANK YOU VERY MUCH FOR YOUR TIME AND PATIENCE IN FILLING OUT THIS QUESTIONNAIRE.

Sensory Irritants: VOCs

Introduction

Exposure to VOCs in nonindustrial settings such as offices typically are to mixtures of many VOCs, each present at concentrations several orders of magnitude below known human threshold levels, i.e., the concentration of first sensation. However, there is considerable evidence that humans experience certain symptoms in the low exposure scenarios. An operating hypothesis is that the sum of concentrations of VOCs elicit the symptoms. There is experimental evidence that supports this hypothesis at TVOC levels on the order of magnitude of 1 - 5 mg m^{-3} or greater (Molhave et al., 1986; Norback et al., 1990; Molhave et al., 1991; Molhave et al., 1993). At levels below these, evidence is contradictory.

The primary hypothesis of this study is that the potencies of the individual VOCs, as well as their total concentration, must be taken into account to relate low level exposures to symptoms. To test this hypothesis requires the development of a single, integrated, relative irritancy scale for VOCs commonly found in indoor environments. To develop this scale, an irritancy database composed of information on various measures of irritancy was assembled. The database included human and animal irritancy measures, as well as key physical properties of the VOCs. To evaluate data available for development of an irritancy scale, some consideration of physiology is also required, as the structure of the sensory apparatus determines how inhaled stimuli from the external environment are translated via the physical mechanisms of the neural networks into reflex responses.

The Common Chemical Sense

The anatomical system that carries (mediates) stimuli responses of the central nervous system (brain and spinal cord) to airborne chemicals (such as VOCs) is the chemosensory system (Tucker, 1971). This system is composed of two elements that are linked, but are distinct from each other: olfaction and common chemical sense. The Cranial Nerve I mediates olfaction (smell) nerve endings in the nose. Olfaction functions mainly as a sensing apparatus to describe the nearby environment. The trigeminal nerve (Cranial Nerve V), which is highly branched with endings scattered through the epithelium of the nasal cavity and cornea (Silver et al., 1986), mediates the common chemical sense, which functions mainly as a warning system. The common chemical sense, first described by Parker (1912), is the sensitivity of the mucosa (ocular, nasal, oral) of the human body to

chemicals (Cometto-Muniz and Cain, 1994). Upper respiratory tract epithelial tissues share the chemical sensitivity of the trigeminal nervous system. The common chemical sense lacks the specialized cells of olfaction; instead, free (unspecialized) nerve endings comprise the chemoreceptive elements of the mucosa (Cain, 1981). Sensations reaching the brain through the trigeminal nerve are pain, temperature, and touch (Tucker, 1971). Vertebrates above fish (Tucker, 1971), and even primitive forms of life (Parker, 1912), have the common chemical sense.

The trigeminal nerve mediates the common chemical sense primarily as a warning system of exposures at irritant thresholds or higher concentrations; however, the chemosensory system has a range rather than a binary on/off response. For example, the common chemical sense operates even at low levels:

> [the trigeminal nerve] .. "was found to contribute to perceived magnitude even when the stimulus was too weak to produce obvious irritation."(Cain, 1976)

and,

> "Even weak common chemical stimuli may eventually evoke pain, a reason why the "chemistry" of this modality has appealed to persons who study air pollution, warning agents, industrial contaminants and agents for crowd control."(Cain, 1981)

Stimulus-Receptor Interaction

The common chemical sense is mediated by the free endings of the trigeminal nerve. Located at the end of a nerve are sites where outside molecules (drugs, sensory irritants, etc.) can interact. These sites are termed "receptors". As described by Vander (1985), the function of receptors in the human body is to translate external information from energy

forms (pressure, temperature, etc.) into action potentials; the process of translating stimulus energy into an electrical response in a receptor is known as transduction.

Receptors are either specialized plasma membranes located at the peripheral endings of nerves, or in the case of the trigeminal nerve, separate cells that affect the peripheral ends of the nerve. In the latter case, the separate receptor cell contains the membrane that is activated by the stimulus (either by chemical reaction or by physical adsorption), and upon stimulation, the receptor cell releases a chemical messenger that diffuses across the extracellular cleft separating the receptor cell from the nerve and binds to specific site on the nerve. The result is an electrical change (a graded potential) in the nerve. Therefore, a stimulus acts upon the membrane of an unspecialized nerve ending to alter its permeability, which results in a graded change in potential at the nerve. As receptor potentials are graded potentials, their magnitude and duration vary with stimulus strength.

Chemicals that interact with receptors cause the release of neuropeptides, which result in transmission of impulses to muscles. One chemical of the class of neuromodulators, the neuropeptide substance P (SP), exists in sensory neurons (Vander, 1985). Release of SP will evoke activation of neurotransmitters (Lundberg et al., 1984). As described by Lu (1991), the most common neurotransmitter is acetylcholine (ACh), a substance secreted by the parasympathetic nerve fibers. Interaction of acetylcholine with its receptors leads to muscle contraction. Acetylcholine esterase (AChE) hydrolyzes acetylcholine to acetic acid and choline, i.e., breaks ACh down to its constituents, resulting in the cessation of

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muscle contraction. Therefore, interference with synaptic transmission by impairing the release of AChE results in buildup of ACh, inducing muscle contractions.

The irritancy response is a stimulus-receptor interaction. Upon inhalation chemicals interact with irritant receptors on the trigeminal nerve. These changes cause the release of the nerve mediators (e.g., Substance P), which evoke activation of cholinergic neurons (causing release of ACh), which results in muscle contractions, reflex responses, and nasal secretion. These complex interactions at the molecular level occur within a short time period (0.1- 1 second). Inhalation of a sensory irritant results in a burning, itching sensation, and the reflexive response of decreased respiration. Conversely, removal of the irritant results in a cessation of the irritant response.

Physical Mechanism of Irritancy

Experimental studies have indicated compounds stimulate an irritant response to the trigeminal nerve through physical and chemical mechanisms. Almost all the VOCs of interest in the current study exert irritancy through a physical mechanism. The physical mechanism of irritancy is governed by an equilibrium between the external concentration in air and the internal concentration of receptor-bound VOC. The relationship is linear over a wide concentration range; as the external concentration increases, the internal receptor-bound VOC concentration increases. This mechanism is reversible; upon removal of the irritant, the VOC-receptor internal concentration decreases with a corresponding decrease in irritancy. For this mechanism, strong relationships are typically observed between the physical properties (e.g., vapor pressure, molecular weight, etc.) of

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the compounds with increasing number of carbon atoms in a straight chain (homologous series), by chemical class.

Some VOCs, typically the lowest member of a homologous series (e.g., formaldehyde), exert their irritancy via a chemical mechanism; the compound binds chemically to the receptor and clearance is via systemic mechanisms. These compounds are generally more chemically reactive (e.g., formaldehyde, acrolein, ethylene). Other than formaldehyde and acrolein (in environmental tobacco smoke) these VOCs generally are not found indoors at concentrations above those in outside air.

Ferguson (1939) summarized toxicity studies of the late 19th and early 20th centuries; he noted that compounds which exerted an irritant effect through physical mechanisms demonstrated close correlations with physical parameters and tended to be compounds of low vapor pressure and high molecular weight. As can be see in Table 20, CHBS VOC vapor pressures are relatively low, within the range of 10^{-1} to 10^3 mm Hg. Included in the table for comparison are other VOCs in the irritancy database, which have vapor pressures within the range of 10^3 to 10^5 (mm Hg). The VOCs with the highest vapor pressures (ethylene, propylene, 1-butene, and formaldehyde) are compounds of greater chemical reactivity.

TABLE 20. Saturated vapor pressure of VOCs (CHBS and 10 VOCs of high vapor pressure)

Reason for Inclusion	Compound	Chemical Class	Saturated Vapor Pressure at 23 C (mm Hg)
CHBS VOCs	n-Dodecane	Alkane	1.92E-01
	1-Phenylethanone	Ketone	3.97E-01
	n-Undecane	Alkane	5.29E-01
	Benzaldehyde	Aldehyde	8.10E-01
	2-Butoxyethanol	Alcohol	1.20E+00
	1,2,3-Trimethylbenzene	Aromatic	1.50E+00
	n-Decane	Alkane	1.53E+00
	Limonene	Terpene	1.78E+00
	1,2,4-Trimethylbenzene	Aromatic	1.89E+00
	1,3,5-Trimethylbenzene	Aromatic	2.42E+00
	2-Ethyltoluene	Aromatic	2.43E+00
	3,4-Ethyltoluene	Aromatic	2.79E+00
	n-Nonane	Alkane	4.14E+00
	o-Xylene	Aromatic	5.82E+00
	Styrene	Aromatic	6.47E+00
	m,p-Xylene	Aromatic	7.45E+00
	Ethylbenzene	Aromatic	8.42E+00
	n-Octane	Alkane	1.22E+01
	Tetrachloroethylene	Chlorinated Alkene	1.67E+01
	Toluene	Aromatic	2.55E+01
	n-Butyl acetate	Ester	3.50E+01
	2-Propanol	Alcohol	3.86E+01
	n-Heptane	Alkane	4.19E+01
	Methylcyclohexane	Alkane	4.25E+01
	Ethanol	Alcohol	5.10E+01
	3-Methylhexane	Alkane	5.75E+01
	Trichloroethene	Chlorinated Alkene	7.16E+01
	Benzene	Aromatic	8.56E+01
	Ethyl acetate	Ester	8.60E+01
	1,1,1-Trichloroethane	Chlorinated Alkane	1.22E+02
	Methylcyclopentane	Alkane	1.36E+02
	n-Hexane	Alkane	1.56E+02
	2-Propanone	Ketone	2.28E+02
	Dichloromethane	Chlorinated Alkane	4.53E+02
	n-Pentane	Alkane	6.07E+02
	Trichlorofluoromethane	Chlorinated Alkane	1.03E+03
Other VOCs in the Irritancy Database	Ethylamine	Amine	1.14E+03
	Dimethylamine	Amine	2.08E+03
	cis-2-Butene	Alkene	2.52E+03
	1,3-Butadiene	Diene	3.07E+03
	Methylamine	Amine	3.13E+03
	1-Butene	Alkene	3.25E+03
	Formaldehyde	Aldehyde	4.31E+03
	Methylchloride	Chlorinated Alkane	6.17E+03
	Propylene	Alkene	1.56E+04
	Ethylene	Alkene	1.16E+05

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Physiological Relationships between Irritancy and Odor

Although the focus of the work reported here is the irritant effect, there are physiological relationships between irritancy and odor that must be considered. Correlations between irritancy and odor are based on physiological connections between the trigeminal and olfactory nervous systems.

Stimuli entering the nasal passages are typically sensed by the olfactory nervous system at concentrations much lower than concentrations sensed by the trigeminal nervous system. The difference in sensing abilities between the two nervous systems is most likely due to physiology. Free endings of the trigeminal nerve lie deeper within the respiratory mucosa than the cilia of the olfactory receptors (Cain, 1988). The stimulus progresses from the air phase to the irritant receptors via the watery and mucoid layers of the mucus. In so doing, there is some attenuation of concentration due to clearance and possible conversion to other products (Cain, 1988).

> "In order to reach the [trigeminal] nerve endings, however, the molecules must pass beneath the region of the respiratory or olfactory cilia and into intercellular spaces .... This difference in the vertical component of molecular migration seems a reasonable account of the difference in the latency between odor and irritation."(Cain, 1981)

The two nervous systems also respond differently to sustained exposures. Although the olfactory system responds first to strong stimuli, it quickly adapts; i.e., olfaction experiences fatigue. After the initial response to strong odors, time-course adaption indicated exponential decay (Cain, 1988). Odor perception is very labile (readily

undergoes change); the percent of subjects who find an odor acceptable is inversely correlated with the odor intensity (Cain, 1982).

Odor mixtures from multiple individual constituents of equal strength add to less than the sum of the individual compounds, i.e., odorants exhibit hypoadditivity (Berglund, 1974; Cain and Drexler, 1974; Cain, 1975; Laing et al., 1984; Cometto-Muniz and Hernandez, 1990; Schiet and Cain, 1990). Some evidence indicates that the most odorous compound will dominate the odor perception of the whole mixture; i.e., individual odor perceptions will be masked by the strongest compounds. The odor quality of binary mixtures is most similar to the strongest individual component (Cain and Drexler, 1974; Laing et al., 1984). Cain and Drexler (1974) also showed that for binary odor mixtures, the stronger odor dominated and sometimes masked completely the odor of the weaker component.

VOC concentrations experienced in nonindustrial occupational exposures are typically low, and irritant receptors are unlikely to be saturated, as researchers report irritancy does not experience fatigue but continues to increase over time. Moncrieff (1967) noted that the fatigue of olfaction does not appear to occur for the common chemical sense. Cain (1981) reported irritancy showed little adaption, and probably even increased with continuing exposure, i.e., irritancy appeared to be cumulative. Hudnell et al. (1992) described their chamber experiment on the time-course functions for exposure of 66 healthy males to a VOC mixture (25 mg m^{-3}). They found that eye and throat irritation increased or showed no adaption during exposure, although odor sensation decreased by 30%. Cometto-Muniz and Hernandez (1990) demonstrated that sensory irritants exhibit both simple additivity,

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and a tendency to hyperadditivity, i.e., the sum of the parts is greater than the whole. Therefore, both observational and chamber studies indicate the irritancy response is composed of the sum of irritation from individual compounds.

Summary

Although irritancy is latent (compared to odor), irritant effects are cumulative, and increase with concentration and time. A mixture of irritant VOCs sums to the total perceived irritation, or even greater than the sum, i.e., irritants exhibit additivity, and even hyperadditivity. Olfaction is limited by the masking of individually strong odors and quickly overlain by fatigue. Odorants exhibit hypoadditivity, i.e., the sum of individual odors is less than the total perceived odor.

Therefore, use of irritant and olfactory data should reflect their physiological differences. The assumption of additive effects for irritancy is supported by experimental evidence; irritant effects are cumulative in low exposure scenarios where the irritant receptor is not saturated. Therefore, it is reasonable to base the irritancy of a mixture on the summation of individual irritant VOC potencies. In contrast, human odor thresholds are not expected to be directly useful in an irritancy scale, although a large amount of data exists on human odor thresholds. However, the relatively consistent relationships between odor and irritancy thresholds can be used to infer missing irritancy information.

Irritancy Bioassays

There is no single, consistent database of human irritancy measures that includes a sufficient number of compounds for the development of a relative irritancy scale based on individual VOC potencies. However, the common chemical sense, as mediated by the trigeminal nerve, controls response to sensory irritants for animals as well as humans. Trigeminal nerve response, therefore, can be used as a surrogate for irritant response. Both animal and human data on trigeminal nerve response exist. Controlled animal experiments on the sensory irritation from stimulation of the trigeminal nerve provide the greatest amount of irritancy data. Animal data are also well correlated with the limited human data.

Animal Irritancy Bioassay

In animals, there are two methods of measuring the effects of chemicals on the trigeminal nerve endings: 1) measurement of the response (neural activity) to direct application of stimuli (electrical or chemical) at high levels (Dawson, 1962; Ulrich et al., 1972; Kulle and Cooper, 1975; Silver et al., 1986); and 2) measurement of respiratory response to inhalation exposures at various levels (Alarie, 1966; American Society for Testing and Materials Standards, 1984). The latter method is more efficient in terms of time and materials. More importantly, methods that evaluate sensory irritation via direct application of chemical or electrical stimuli use concentrations high enough to cause tissue damage, and are inherently less desirable. Alarie noted that airborne concentrations below levels causing tissue damage caused irritant responses of the upper and lower respiratory systems. Therefore, Alarie developed a method that evaluates typical upper respiratory

responses caused by trigeminal nerve stimulation, i.e., the reflex inhibition of respiration upon exposure to a sensory irritant. Alarie's original method (1966) became the standardized approach (American Society for Testing and Materials Standards, 1984) to estimate the sensory irritancy of airborne chemicals.

Inhalation of a sensory irritant induces several reflex responses. The upper airway (nasal cavity, trachea) and the lower airway (all structures below the larynx to the alveoli) comprise the respiratory system (Alarie, 1973). Alarie (1966) reports that the overall response to sensory irritants in the upper airway is a decrease in the respiratory rate; in the lower airway, irritants stimulate an increase in the respiratory rate. Irritating compounds administered only to the **upper** airway (trachea cannulated[1] mice) stimulate reflex responses of: a decrease in the breathing rate; an increase in the duration of expiration; a transient increase of respiratory rate, from time to time, sometimes accompanied by body movements; spasm(s) of the larynx and bronchi; an increase in the bronchial tone; a decrease in pulmonary ventilation; a decrease in pulse rate; an increase in blood pressure; a decrease in pulmonary blood flow; short onset time of the reactions; reactions which usually disappeared as soon as the administration of the compound was terminated. Typical responses of **lower** airway irritation are (Alarie, 1966): no change in heart rate; no change or slight decrease in blood pressure; an increase in breathing rate; an increase in pulmonary ventilation; longer onset and duration of the reaction.

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1. Cannulation refers to surgical severing.

Stimulation (chemical or electrical) of the trigeminal nerve in humans or animals causes a

reflex pause in respiration following the expiratory phase, termed "momentary apnea"

(Cometto-Muniz and Cain, 1992). This response can be measured and quantified, as seen
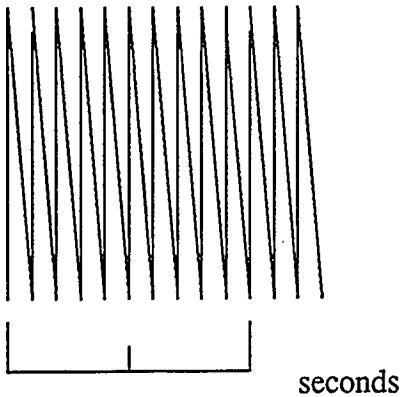
FIGURE 9. a. Typical oscillograph
display showing respiratory cycle for
control conditions
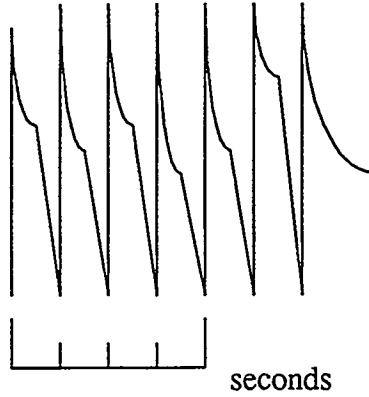
FIGURE 9. b. Typical oscillograph
display showing respiratory cycle for
exposure to a sensory irritant

in Figure 9a (control) and Figure 9b (exposure)[1]. The upstroke of the trace is the

inhalation, the downstroke the exhalation. Animals exposed to sensory irritants show a

marked pause after inhalation and before exhalation, as seen in Figure 9b. A whole body

plethysmograph[2] with airtight seals quantifies the response of animals exposed to sensory

irritants. A transducer measures pressure changes due to respiration, which are displayed

on an oscillograph. The concentration of airborne irritant causing a 50% decrease in·

respiratory rate (RD_{50}) is determined from the concentration response curve from

experiments of four mice simultaneously exposed to each concentration (American

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1. Adapted from Figure 1 in (Kane et al., 1979).

2. Body plethysmograph is a cylindrical, airtight tube with room for head to project into the study space.

Society for Testing and Materials Standards, 1984). Upon removal of the animals from exposure, respiratory rate returns to normal.

Figure 10 presents reported RD_{50} values for VOCs versus increasing number of straight-chain carbon atoms and by chemical class for those classes typically found indoors. The most irritating compounds are those with the lowest RD_{50} concentrations. RD_{50} values range over three orders of magnitude. As first members of each homologous series are typically controlled by chemical mechanisms of potency, these compounds were excluded.

The compounds in Figure 10 all exert an irritant effect via a physical mechanism. Potency, as measured by RD_{50} concentrations, increases with increasing carbon chain length within alcohols (C_2-C_5, ethanol to 1-pentanol) (Kane et al., 1980), aldehydes (C_2-C_6, 1-propanal to 1-hexanal) (Alarie, 1981; Steinhagen and Barrow, 1984), amines (C_2-C_7, ethylamine to 1-heptylamine) (Nielsen and Vinggaard, 1988; Gagnaire et al., 1989), aromatics (C_2-C_6, ethylbenzene to 1-hexylbenzene) (Nielsen and Alarie, 1982), and ketones (C_3, C_5, C_7) (Kane et al., 1980; DeCeaurriz et al., 1981; Schaper, 1993).

Available RD_{50} data for alkanes and esters do not show positive correlations with increasing number of straight-chain carbons; however, these results are probably exceptions due to data limitation. For the alkanes (not shown), RD_{50} values were available for only 3 compounds (*n*-heptane, *n*-octane and *n*-nonane). The RD_{50} values for the two higher molecular weight compounds were extrapolated by the investigators from a
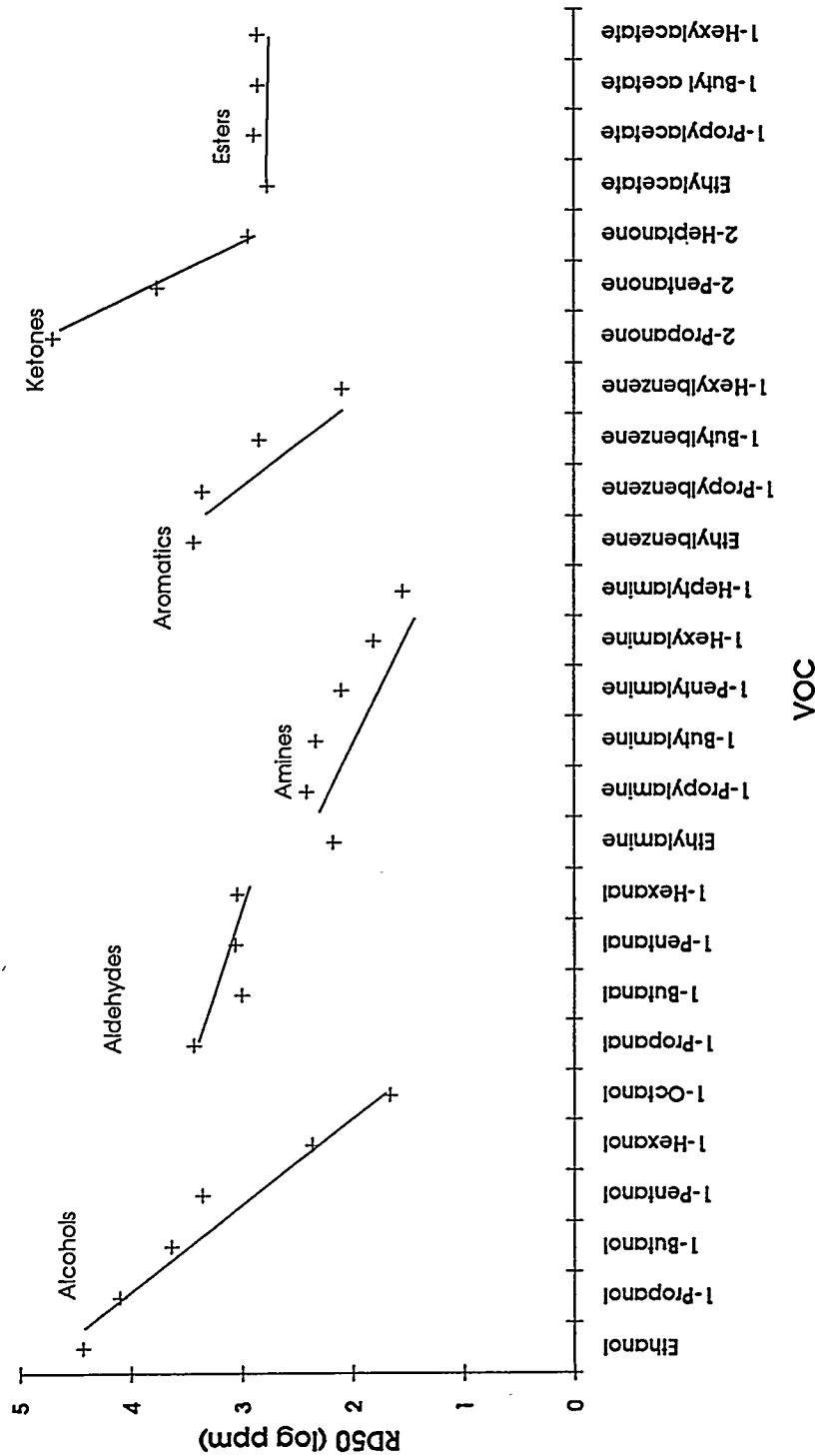
FIGURE 10. Physical Mechanisms: RD_{50} (log ppm) by increasing carbon atoms in straight-chain series, by chemical class

regression equation as the measure of irritant effect (RD_{50}) could not be reached; 40% was the maximum decrease in the respiratory rate that could be achieved for *n*-octane and *n*-nonane (Kristiansen and Nielsen, 1988). Although RD_{50} values for four compounds of straight-chain carbons were available for esters (ethylacetate, 1-propylacetate, 1-butylacetate, 1-hexylacetate), the data did not show a definite trend. Additional information (e.g., mouse bioassays, or other measures of irritant effect) would be required to understand if and why the ester and alkane chemical classes are exceptions to the general rule of increased potency with increased number of straight-chain carbon atoms, or if the slope of the line is very small and cannot be estimated within experimental uncertainties.

Human Pungency Threshold

A limited amount of data exists on the first sensation of trigeminal response perceived by humans; i.e., the *threshold* concentration. The threshold level of sensory irritation is termed the *pungency* threshold. Pungency threshold is the most appropriate measure of an individual VOC's potential to be irritating to humans; however, data on human pungency thresholds is extremely limited - just 20 compounds across 3 chemical classes. Additionally, due to the functional interconnection between olfaction and pungency, humans distinguish with difficulty between olfactory and pungent sensations. Even when researchers use a 'pure' odorant, the extent of trigeminal nerve contribution is uncertain in typical olfaction experiments, as both odor and trigeminal nerves contribute to the sense of

smell. Researchers have been able to evaluate separate pungency and odor thresholds by testing agents with subjects who have a sense of smell and subjects that do not.

Researchers 'present' a compound to a subject, either by direct contact with one or another nostril or by inhalation of a vapor, and note when a compound is first sensed, i.e., when a threshold of nasal sensation is reached. For normal individuals (normosmics), olfaction is the first nasal sensation triggered. Individuals who lack a sense of smell (anosmics), either through trauma or being unable to smell since birth, are still able to detect chemical vapors; these humans sense airborne compounds through stimulation of the trigeminal nerve. Threshold anosmic nasal sensations are pungency thresholds.

Doty et al. (1975) used anosmics and normosmics to differentiate between pungency and olfaction. In general, compounds detected by anosmics (pungent) differed from compounds not detected (odorous) based on several parameters. Compounds detected by anosmics are on the whole smaller in molecular weight, higher in water solubility, higher in vapor pressure, lower in boiling point, and possess larger dipole moments. Thresholds for chemicals detected by the anosmics are approximately two log volume concentration units above those of normals; that is, pungency thresholds are on the order of 100 times higher than odor thresholds.

Doty et al. (1978) developed a complete, replicable methodology of pungency threshold determination. Anosmics and normosmics sense randomized compounds and report threshold nasal sensations. To insure relatively uniform stimulus presentation, the top of a

sniff bottle is placed, immediately upon opening, under the nose of the subject. The subject's eyes are closed (to avoid corneal trigeminal nerve stimulation (Dawson, 1962)) and a clean paper towel is positioned under the nose and over the mouth to prevent contamination of mustaches or skin. A full trial consists of 3-second presentation of two compounds, the tested compound and an equivalent amount of the reference compound[1]. The subject is to state which of the two were stronger. Six to 10 detection trials are used for each substance. Correct detection of all but 1 or 2 of the trials determine stimulus detection. On the basis of this procedure, researchers determined pungency thresholds within 3 of chemical classes (alcohol, ketone, ester).

Two important points can be drawn from the results from the normosmic/anosmic studies. First, odor thresholds are typically about two orders of magnitude below pungency thresholds (Doty, 1975; Doty et al., 1978; Cometto-Muniz and Cain, 1990; Cometto-Muniz and Cain, 1991; Cometto-Muniz and Cain, 1992; Cometto-Muniz and Cain, 1994). The separation between the two thresholds indicates functional differences between olfaction and irritancy of sensing and warning, respectively.

Second, odor and pungency thresholds decrease logarithmically with carbon chain length for homologous alcohols (Cometto-Muniz and Cain, 1990), homologous esters (Cometto-Muniz and Cain, 1991), and homologous alcohols, esters[2] and ketones (Cometto-Muniz and Cain, 1994). Pungency thresholds for anosmics, and to a much lesser extent odor

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1. Propylene glycol was used as the reference compound. No rationale was given for choice of compound.
2. The logarithmic decrease of odor and pungency thresholds with carbon chain length is much smaller for esters, as compared to the alcohols and ketones (Cometto-Muniz and Cain, 1994).

thresholds of normosmics, are highly correlated with vapor pressure (Cometto-Muniz and Cain, 1990; Cometto-Muniz and Cain, 1991; Cometto-Muniz and Cain, 1994).

Where such a physical equilibrium exists, the thermodynamic activity should be the same in all phases, although the absolute concentration in each phase will vary. The calculated thermodynamic activity of an airborne chemical is the ratio of partial vapor pressure of a substance at some threshold concentration over the saturated vapor pressure of the substance, $(\frac{P_t}{P_o})$, assuming the vapor behaves as an ideal gas. For nasal pungency, thermodynamic activity plotted against carbon chain length remains roughly equivalent for straight-chain alcohols across 1 to 8 carbon chain lengths (Cometto-Muniz and Cain, 1990) and up to decyl and dodecyl acetates[1] (Cometto-Muniz and Cain, 1991), although this is not the case for odor thresholds.

Threshold Limit Values (TLVs)

The American Conference of Governmental Industrial Hygienists (ACGIH) has developed biological exposure indices, referred to as Threshold Limit Values (TLVs). TLVs are concentrations to which healthy (male) workers can be exposed for 8 hours per day during a typical work week and not experience adverse effects. In principle, TLVs determine "safe" levels as per various endpoints. The basis on which the TLVs were established varies depending upon substance, and includes protection against health impairment due to irritation, narcosis, nuisance, and more recently, cancer. Current TLVs

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1. These results from only one anosmic.

are set to protect humans from exposure to carcinogens as well as the original basis of sensory irritation. Safety thresholds (TLVs) for carcinogens, however, are much lower than those for irritancy, in order to protect individuals from extrapolated cancer risks due to lifetime exposures.

There are problems with use of this data for the irritancy scale. First, more than half of TLVs are based on different endpoints than sensory irritation (Alarie, 1981). Second, TLVs are based on a wide range of different experimental data, with no specified methodology. Finally, as is explicitly stated by the ACGIH, TLVs are not threshold levels for human sensory irritation but guidelines of occupational safety (American Conference of Governmental Industrial Hygienists, 1992). Roach and Rappaport (1990) reviewed the documentation for the airborne concentration of substances that reflected concentrations to which nearly all healthy workers may be repeatedly exposed without adverse effect. They report that many TLVs are above the comfort level of the individuals upon whose experiences the TLVs were developed; specifically, "... overall, 14% of the employees exposed at or below the 1986 TLV were adversely affected." Roach and Rappaport found that many of the TLVs were not correlated with the number of humans adversely effected, but the TLVs were correlated with the levels which were perceived at the time to be achievable by industry. Therefore, use of the TLVs in irritancy analysis is tempered with the knowledge that the TLVs are designed to provide a margin of safety for *occupational* exposures, but they are not actually thresholds in the definition of the first nasal sensation (threshold) of response.

Due to these limitations, TLVs cannot be used directly in an irritancy scale. However, the TLVs still contain some information on human sensory irritation useful for testing the feasibility of using an animal model to approximate human irritancy.

Researchers hypothesized that an animal model based on the RD_{50} response is useful in prediction of human irritancy response, and therefore useful in development of acceptable exposure limits to airborne chemical irritants (i.e., TLV guidelines). Frazer (1953) stated that if the primary pharmacological (and by extension, toxicological) action of a substance was well defined, factors of 10 based on an animal model could reliably predict other levels of effect; e.g., a lethal dose is four orders of magnitude greater than an acceptable dose (1/10,000). Rationalization for the use of an animal (mouse) model to predict human responses is based on the following: 1) the anatomic and physiological basis of the measured response; 2) the easily recognizable and quantifiable response of decrease in respiration; 3) the observed dose-response relationship; 4) the correspondence between the effect observed in animals and the effect reported by human subjects, that is, a burning sensation of the eyes, nose and throat (Alarie et al., 1981).

Researchers have found that the animal (mouse) model can be used to predict acceptable levels of exposure for humans (Alarie, 1973; Barrow et al., 1977; Kane and Alarie, 1977; Barrow et al., 1978), even where exposure concentrations varied over five orders of magnitude (Kane et al., 1979). Consequently, researchers predicted that "safe" human exposure concentrations to sensory irritants are roughly two orders of magnitude below

animal RD_{50} levels; therefore, "safe" human exposures should correlate well with animal RD_{50}s.

Existing industrial exposure guidelines (TLVs) correlated with predicted "safe" levels of exposure based on the animal measure (RD_{50}). Analyses of earlier data were based on relatively few compounds: 25 airborne chemicals across various chemical classes and spanning five orders of magnitude (Alarie, 1981), 10 alkyl benzenes (Nielsen and Alarie, 1982), and 8 aliphatic amines (Gagnaire et al., 1989).

The analysis presented here also demonstrates strong correlations between RD_{50} and TLV values, and utilizes a larger amount of data - all VOCs for which RD_{50}s and TLVs were available (30-60 compounds). 1980 TLVs were used to focus on TLVs set primarily for endpoints of sensory irritation, as well as the more recent 1992-93 TLVs. Table 21 lists compounds for which animal RD_{50} values, 1980 TLVs and 1992-93 TLVs were available. Table 22 reports Pearson correlations (two-tailed, $p < 0.01$) between the animal RD_{50}s and human TLVs (1980 and 1992-93). The correlations between RD_{50} values and the actual values used in industrial exposures for the 1980 TLVs (0.90) are only slightly higher than the correlations for the 1992-93 TLVs (0.88). The more recent TLVs include 2 compounds (ethyl acrylate and formaldehyde) with TLVs set to protect workers from cancer, 2 compounds (acetaldehyde and *p*-dichlorobenzene) with proposed decreases due to designation as an animal carcinogen, and 1 compound (styrene) suspected to be a human carcinogen based on other sources. The stronger correlation ($r = 0.90$) between RD_{50}

TABLE 21. RD$_{50}$ (ppm), 1992-1993 TLV (ppm), 1980 TLV (ppm)[a], by chemical class and abstract number

Compound	Chemical Class	Chemical Abstract Number	RD$_{50}$ (ppm)	TLV (ppm) 1992-1993 ACGIH	TLV (ppm) 1980 ACGIH
Acetaldehyde	Aldehyde	00075-07-0	3.4E+03	1.0E+02	1.0E+02
Acetic acid	Carboxylic Acid	00064-19-7	3.7E+02	1.0E+01	NA
Acrolein	Aldehyde	00107-02-8	2.5E+00	1.0E-01	1.0E-02
Allylalcohol	Allyl	00107-18-6	2.7E+00	2.0E+00	2.0E+00
Allylchloride	Allyl	00107-05-1	2.0E+03	1.0E+00	NA
Benzylchloride	Chlorinated Aromatic	00100-44-7	2.2E+01	1.0E+00	NA
n-Butanol	Alcohol	00071-36-3	4.4E+03	5.0E+01	5.0E+01
2-Butoxyethanol	Alcohol	00111-76-2	2.8E+03	2.5E+01	2.5E+01
n-Butylacetate	Ester	00123-86-4	7.3E+02	1.5E+02	1.5E+02
tert-Butylacetate.	Ester	00540-88-5	1.6E+04	2.0E+02	2.0E+02
n-Butylamine	Amine	00109-73-9	2.2E+02	5.0E+00	5.0E+00
p-tert-Butyltoluene	Aromatic	00098-51-1	3.6E+02	1.0E+01	NA
Chlorobenzene	Chlorinated Aromatic	00108-90-7	1.1E+03	1.0E+01	NA
α -Chlororacetophenone	Ketone	00532-27-4	9.6E-01	5.0E-02	5.0E-02
Cyclohexanone	Ketone	00108-94-1	7.6E+02	2.5E+01	2.5E+01
o-Dichlorobenzene	Chlorinated Aromatic	00095-50-1	1.8E+02	2.5E+01	NA
p-Dichlorobenzene	Chlorinated Aromatic	00106-46-7	1.8E+02	7.5E+01	NA
Diethylamine	Amine	00109-89-7	1.9E+02	1.0E+01	NA
Diisobutylketone	Ketone	00108-83-8	2.9E+02	2.5E+01	NA
Diisopropylamine	Amine	00108-18-9	1.6E+02	5.0E+00	NA
Dimethylamine	Amine	00124-40-3	3.9E+02	1.0E+01	1.0E+01
Ethanol	Alcohol	00064-17-5	2.7E+04	1.0E+03	1.0E+03
Ethylacetate	Ester	00141-78-6	6.0E+02	4.0E+02	4.0E+02
Ethylacrylate	Acrylate	00140-88-5	3.2E+02	5.0E+00	NA
Ethylamine	Amine	00075-04-7	1.5E+02	1.0E+01	1.0E+01
Ethylbenzene	Aromatic	00100-41-4	2.8E+03	1.0E+02	1.0E+02
Formaldehyde	Aldehyde	00050-00-0	1.0E+01	3.0E-01	2.0E+00
Furfural	Aldehyde	00098-01-1	2.9E+02	2.0E+00	2.0E+00
n-Heptane	Alkane	00142-82-5	1.7E+04	4.0E+02	NA
2-Heptanone	Ketone	00110-43-0	8.9E+02	5.0E+01	5.0E+01
Isoamylalcohol	Alcohol	00123-51-3	2.6E+03	1.0E+02	1.0E+02
Isobutylalcohol	Alcohol	00078-83-1	1.8E+03	5.0E+01	NA
Isopropylacetate	Ester	00108-21-4	4.3E+03	2.5E+02	2.5E+02
Isopropylamine	Amine	00075-31-0	1.6E+02	5.0E+00	5.0E+00
Methanol	Alcohol	00067-56-1	3.3E+04	2.0E+02	2.0E+02
5-Methyl-2-hexanone	Ketone	00110-12-3	1.2E+03	5.0E+01	NA
Methylacetate	Ester	00079-20-9	8.3E+02	2.0E+02	2.0E+02
Methylamine	Amine	00074-89-5	1.4E+02	5.0E+00	1.0E+01
Methylethylketone	Ketone	00078-93-3	1.7E+04	2.0E+02	NA
Methylisobutylketone	Ketone	00108-10-1	3.2E+03	5.0E+01	5.0E+01
α -Methylstyrene	Allyl	00098-83-9	2.7E+02	5.0E+01	NA
n-Nonane	Alkane	00111-84-2	6.2E+04	2.0E+02	2.0E+02
n-Octane	Alkane	00111-65-9	1.8E+04	3.0E+02	3.0E+02
n-Pentanal	Aldehyde	00110-62-3	1.2E+03	5.0E+01	5.0E+01
2-Pentanone	Ketone	00107-87-8	5.9E+03	2.0E+02	2.0E+02
Pentylacetate	Ester	00628-63-7	1.5E+03	1.0E+02	NA
Phenol	Phenol	00108-95-2	1.7E+02	5.0E+00	NA
n-Propanol	Alcohol	00071-23-8	1.3E+04	2.0E+02	2.0E+02
2-Propanol	Alcohol	00067-63-0	1.1E+04	4.0E+02	4.0E+02
2-Propanone	Ketone	00067-64-1	5.1E+04	7.5E+02	7.5E+02
Propylacetate	Ester	00109-60-4	7.9E+02	2.0E+02	2.0E+02
Styrene	Aromatic	00100-42-5	5.7E+03	5.0E+01	5.0E+01
Toluene	Aromatic	00108-88-3	4.5E+03	5.0E+01	NA
Toluene2,4-diisocyanate	Isocyanate	00584-84-9	3.4E-01	5.0E-03	5.0E-03
Triethylamine	Amine	00121-44-8	1.7E+02	1.0E+01	2.5E+01
p-Xylene	Aromatic	00106-42-3	1.3E+03	1.0E+02	1.0E+02
o-Xylene	Aromatic	00095-47-6	1.5E+03	1.0E+02	NA

a. NA indicates guideline not developed as of that year.

TABLE 22. Pearson correlations[a] for RD_{50} (log ppm) and 1980 TLVs (log ppm), RD_{50} (log ppm) and 1992-1993 TLVs (log ppm)

Threshold Limit Values	RD_{50} (log ppm)	Number of Compounds
1980 TLVs (log ppm)	0.90**	37
1992-1993 TLVs (log ppm)	0.88**	57

a. ** - Significance level p < 0.01, two-tailed.

values and 1980 TLVs - which utilizes a smaller number of compounds (N = 37) - reflects the original basis of TLVs as protection against sensory irritants.

Other Available Data

Human odor threshold data are much more extensive than either animal or human irritancy data. In a recent book, Devos et al. (1990) report olfactory thresholds for 641 airborne chemicals, gathered from 372 references that the authors standardized, i.e., made as homogeneous as possible over different researchers and testing conditions. Odor thresholds comprise the greatest amount of data; however, sensory irritation - not olfaction - is the endpoint of interest for this investigation of SBS symptoms in office workers. Nonetheless, human odor and irritancy thresholds are closely related physiologically; the relatively constant relationship that exists between the two thresholds could be used in the development of the irritancy scale.

The fourth and final type of data is the simple physical parameter of vapor pressure. Ferguson (1939) showed a relationship between vapor pressure and narcotic compounds. Nielsen and Alarie (1982) showed vapor pressure predicted sensory irritation potency up

to a chain length of C_6 by chemical class. In a review paper on animal assays for upper airway irritation, Nielsen and Alarie (1992) discuss the use of physiochemical characteristics (structure-activity relationships) to predict the irritating potency of vapors (Nielsen and Alarie, 1992). More recently, research by Cometto-Muniz and Cain (1991, 1994) also indicated olfaction and pungency may be related to simple physical properties such as vapor pressure. Therefore, it is reasonable to use vapor pressure data, and to explore the relationships between vapor pressure and the various measures of sensory stimulation for the purpose of developing a single relative irritancy scale for VOCs commonly found in indoor air.

Correlations Among Irritancy Data by Chemical Class

Human irritancy data (pungency thresholds) are insufficient to develop an irritancy scale for use in a model of SBS. However, several measures of irritation exist, and correlations among irritancy data may be useful in developing a single integrated relative irritancy scale. VOCs commonly found indoors exert their irritancy mainly through physical mechanisms. Additionally, animal RD_{50} values, which are correlated with human occupational guidelines (TLVs), are controlled mainly through physical mechanisms. Therefore, only those compounds that exert their irritant effect through physical mechanisms were included in the correlation analysis. Due to limitations discussed above, TLV was not used in development of the irritancy scale. However, as TLVs contain information on sensory irritation, correlations between TLVs and irritancy measures are also included in the correlation analysis.

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Pearson correlation coefficients were calculated between the logarithms of the

toxicological measure of animal irritancy (RD_{50}), human pungency threshold (P_T), human

odor threshold (O_T), and vapor pressure (VP). Table 23 presents correlations for all classes

TABLE 23. Pearson correlation coefficient (r)[a], number of compounds (N)[b] across irritancy measures and chemical class[c]

Chemical Class	RD_{50} & P_T		RD_{50} & O_T		RD_{50} & VP		P_T & O_T		P_T & VP		O_T & VP	
	r	N	r	N	r	N	r	N	r	N	r	N
All Classes	0.53*	18	0.37**	67	0.12	54	0.87**	20	0.96**	18	0.48**	87
Alcohol	0.94**	8	0.82**	11	0.93**	11	0.96**	11	0.97**	11	0.93**	15
Aldehyde	NA	NA	0.47	8	NA	NA	NA	NA	NA	NA	0.98*	4
Ketone	0.99	3	0.82*	8	0.91*	6	0.99*	3	0.99	3	0.90*	6
Ester	-0.37	7	-0.07	7	-0.1	5	0.91*	6	0.89	4	0.99**	6
Alkane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.92**	9
Aromatic	NA	NA	0.87	5	0.68	8	NA	NA	NA	NA	0.78*	8
Alkene	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.96*	4
Chlorinated Alkane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.86*	7
Chlorinated Aromatic	NA	NA	0.88	4	0.85	4	NA	NA	NA	NA	0.90	4

a.   *   Significance level $p < 0.05$, two-tailed.

     **   Significance level $p < 0.01$, two-tailed.

b. N of all classes not necessarily equal to N summed by chemical class. Table 23 presents classes commonly found indoors, whereas *all* available data are included in correlations for all classes.

c. NA indicates coefficient could not be calculated.

combined, as well as correlations for the individual chemical classes, with number of

compounds and significance levels. The coefficients were calculated in order to 1) test

whether the four response measures were correlated, 2) look for internal consistency

across the four measures, 3) look for consistency in extent and direction of correlation,

and 4) provide a means of estimating missing irritancy thresholds for individual VOCs.

Results varied depending upon the measure and chemical class, and are plotted for clarity

in Figure 11.

Log-Log
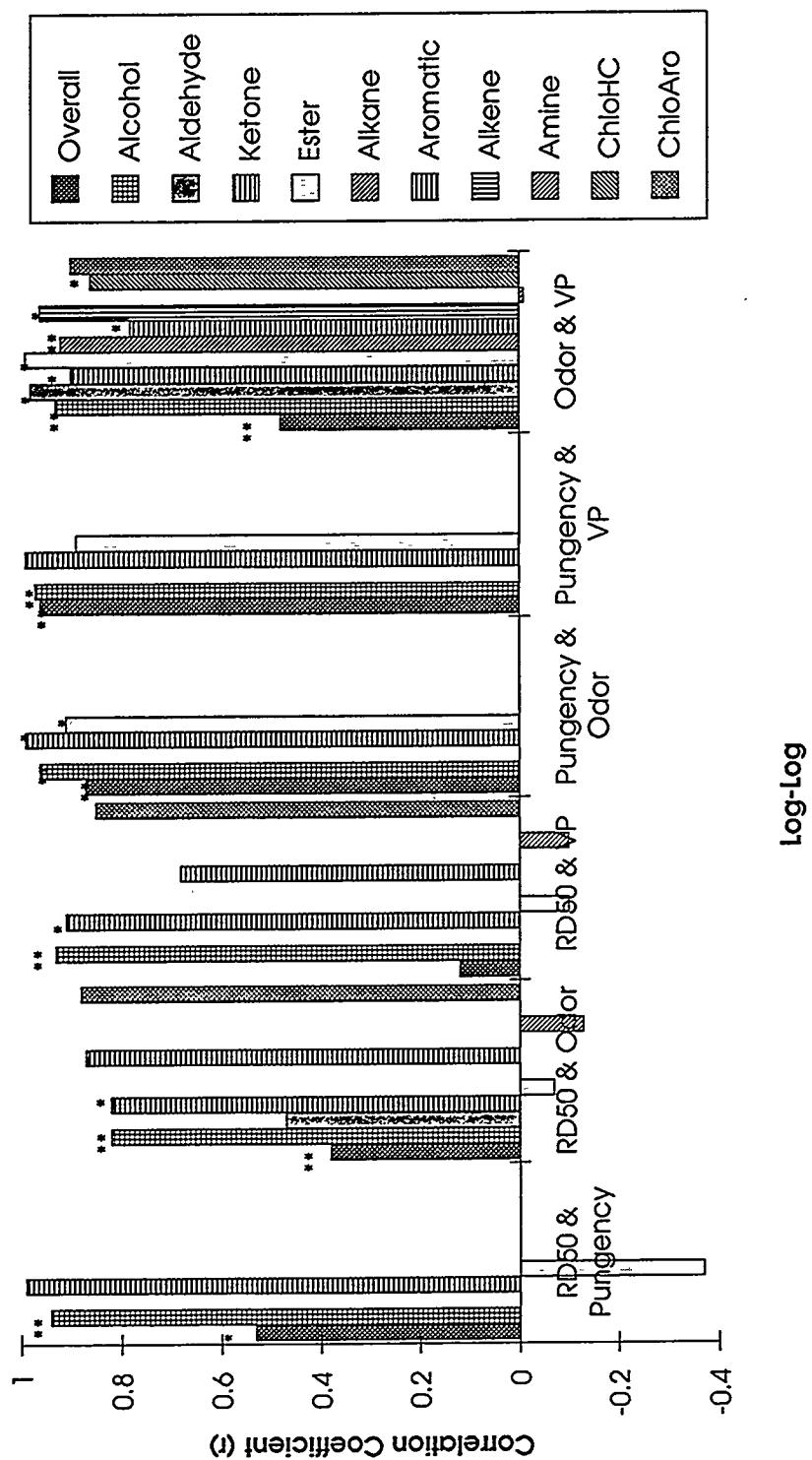
FIGURE 11. Correlations[1] by Chemical Class: Animal, Human and Physical Data

1. * - p < 0.05; ** - p < 0.01. (See Table 23 for N.)

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Two classes commonly found indoors are not represented in Table 23. Correlations could not be calculated for the chlorinated alkene class (tetrachloroethylene and trichloroethene) and for the terpene class (limonene and menthol), as each class had only two compounds. Also, P_T compounds are few in number and are from a single research group (Cometto-Muniz and Cain). By comparison, O_T compounds are numerous and from a diverse number of researchers (Devos et al.'s summary of 372 references).

Table 23 and Figure 11 indicate clearly that chemical class is important. Compared to correlations by chemical class, correlations based on all compounds combined (all classes) are generally less significant statistically.

The animal irritancy measure, RD_{50}, correlated well with the human irritancy measure and human odor thresholds. RD_{50} and P_T were positively and statistically significantly correlated across all classes for 18 compounds (0.53; $p < 0.05$) and within the alcohol class ($r = 0.94$; $p < 0.01$), and positively correlated (not statistically significant due to small number of compounds) for the ketone class (0.99). RD_{50} and O_T were positively and statistically significantly correlated for the alcohol ($r = 0.82$; $p < 0.01$) and ketone ($r = 0.82$; $p < 0.05$) chemical classes, and positively but not significantly correlated for aldehyde (0.47), aromatic (0.87) and chlorinated aromatic (0.88) classes.

Vapor pressure also correlated significantly with animal irritancy responses for several individual classes, but not for all classes combined ($r = 0.12$). RD_{50} and VP were highly and significantly correlated within alcohol ($r = 0.93$; $p < 0.01$) and ketone ($r = 0.91$; $p <$

0.05) chemical classes, and positively but not significantly associated within the aromatic (0.68) and chlorinated aromatic (0.85) classes.

Human irritancy and odor thresholds (P_T & O_T) correlated strongly. Although the number of pungency thresholds was relatively small (20), correlations for all classes were high (0.87) and statistically significant at the $p < 0.01$ level. P_T and O_T were strongly, positively, and significantly correlated within the alcohol ($r = 0.96$; $p < 0.01$), ketone ($r = 0.99$; $p < 0.05$) and ester ($r = 0.91$; $p < 0.05$) chemical classes.

As shown in Figure 12 to Figure 14 in Appendix B, potency increased with increasing carbon chain length (or increasing number of carbons), decreasing vapor pressure, and increasing molecular weight, from methanol to octanol (C_1-C_8 alcohols), 2-propanone to 2-heptanone (C_3-C_7 ketones), and methylacetate to propylacetate (C_1-C_3 esters). Across the three chemical classes, a concentration separation was observed between P_T and O_T, with P_T about 100 to 1000 greater than O_T.

Human irritancy and odor thresholds were found to be strongly correlated with vapor pressure. Correlations were high between P_T and VP for the alcohols, ketones and esters ($r > 0.9$). O_T and VP are significantly correlated for all classes combined (0.48; $p < 0.01$), and there were significant and strong correlations by chemical class ($r > 0.8$; $p < 0.05$), except for the chlorinated aromatics with only 4 compounds).

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The usefulness of VP in the prediction of human irritancy and odor thresholds has been previously noted by several investigators. Ferguson (1939), in his review of the work of a number of investigators, found strong correlations between vapor pressure and narcotic effects. More recently Cometto-Muniz and Cain (1994) noted good correlations between human pungency and odor thresholds observed in their studies of 20 VOCs and vapor pressure.

Available data (not shown) for the *n*-alkanes showed negative correlations between RD_{50} vs. P_T, O_T and VP; however, 2 of 3 RD_{50} values were extrapolated from the bioassay results at values below the 50% reduction in respiratory rate, and may not be accurate. RD_{50} values for *n*-alkanes were reported only for C_6, C_8 and C_9 by Kristiansen and Nielsen (1988). The researchers noted the *n*-alkanes C_8-C_{11} were not able to produce the RD_{50} response level, and extrapolated the RD_{50} values for compounds C_8 and C_9 from the regression slope for lower response levels of each compound. Evidence that the negative relationship between RD_{50} and increasing number of straight-chain carbons is probably due to uncertainties in the values rather than a difference in the underlying mechanism comes from studies of odor. A positive correlation was observed between O_T and VP for increasing number of straight-chain carbons up to *n*-decane (r = 0.92; p < 0.01); i.e., a linear trend between odor threshold and a physical parameter such as vapor pressure indicates a physical mechanism. However, this relationship did not appear to hold for compounds above C_{10}. As the linear trend between vapor pressure and number of carbon atoms failed, so too did the relationship between odor threshold and increasing carbon

atoms in an homologous chain. Due to the close relationship between odor and pungency, it is likely that there are parallels in the physical mechanisms observed for odor and pungency thresholds, and it is likely the same limitations also apply. Therefore, as O_T follows a linear relationship with VP up to C_{10}, it is reasonable to expect RD_{50} to follow a linear relationship with VP up to C_{10}. For the RD_{50} effect, however, the linear trend between vapor pressure and number of carbon atoms appears to have failed lower on the homologous chain, as compounds C_8 and C_9 were not able to produce the RD_{50} effect. Therefore the observed relationships between RD_{50} vs. P_T, O_T and VP were considered not valid given the extremely limited range of currently available RD_{50} data below C_{10} (3 values), and these data were not included in the overall analysis[1].

The small negative correlations between RD_{50} vs. P_T, O_T and VP for esters may also have been due to the limited RD_{50} data available for this chemical class. Human data suggest that the relationship between log P_T and number of carbons does not have a very large slope (Cometto-Muniz and Cain, 1994). If the underlying relationship between irritancy and number of carbon atoms has a small slope and uncertainties are taken into account, the data could give a slightly negative or slightly positive slope. Evidence that the small negative correlations do not represent a difference in the underlying mechanism (i.e., a chemical rather than a physical mechanism) comes from other human studies on pungency and the correlations within this class. For the same set of straight-chain compounds

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1. However, as will be shown, these findings have little impact on the irritancy scale as the alkanes have the highest RD_{50}s; i.e., very high RD_{50} concentrations are required to cause irritant effects.

(methylacetate to butylacetate), human pungency thresholds decreased logarithmically with carbon chain length for homologous esters (Cometto-Muniz and Cain, 1991; Cometto-Muniz and Cain, 1994). Correlation between a physical property and human pungency threshold (VP and P_T; r = 0.89), as well as between a physical property and human odor threshold (VP and P_T; r = 0.99; p < 0.01) indicated that a physical mechanism underlies the irritant effect of the ester class. Therefore, evidence from other measures of potency suggests that the results from the RD_{50} experiments with esters were likely to be an exception due to limited available data.

Pearson correlation coefficients were also calculated between the logarithms of the 1980 Threshold Limit Values (TLVs) and the four measures (RD_{50}, P_T, O_T and VP), and are presented in Table 24. This analysis shows that for individual chemical classes, the older

TABLE 24. Pearson correlation coefficient (r)[a], number of compounds (N)[b] across irritancy measures and chemical class[c], 1980 TLVs (log ppm), RD_{50} (log ppm), O_T (log ppm), P_T (log ppm), VP (log ppm)

Chemical Class	TLV & RD_{50}		TLV & P_T		TLV & O_T		TLV & VP	
	r	N	r	N	r	N	r	N
All Classes	0.90**	37	0.66*	14	0.39**	47	0.21	48
Alcohol	0.79*	7	0.63	5	0.74*	8	0.83*	8
Aldehyde	0.99*	3	NA	NA	NA	NA	NA	NA
Ketone	0.99**	5	0.99	3	0.95*	4	0.88*	5
Ester	-0.12	6	0.46	6	0.35	5	0.29	5
Alkane	NA	NA	NA	NA	NA	NA	NA	NA
Aromatic	0.88	3	NA	NA	NA	NA	NA	NA
Alkene	NA	NA	NA	NA	NA	NA	NA	NA
Chlorinated Alkane	NA	NA	NA	NA	0.97	3	0.77	4
Chlorinated Aromatic	NA	NA	NA	NA	NA	NA	NA	NA

a.   *   Significance level p < 0.05, two-tailed.

     **   Significance level p < 0.01, two-tailed.

b. N of all classes not necessarily equal to N summed by chemical class. Table 24 presents classes commonly found indoors, whereas *all* available data are included in correlations for all classes.

c. NA indicates coefficient could not be calculated.

TLV values (which are more strongly based on sensory irritation) were highly correlated with animal irritancy (RD_{50}) and human pungency (P_T) measures, but were not as strongly correlated with measures that did not directly measure irritancy (O_T and VP). Correlations were stronger by individual classes, especially for the ketones. Note that for TLV and RD_{50} in the ester chemical class, correlations were again anomalously negative (and again the slope was fairly flat) compared to correlations between TLV values and the other measures.

The forgoing discussion has demonstrated the interrelationships across, and the strengths and weaknesses of, different types of data. Human pungency thresholds most closely approximate the information required, but available data are extremely limited. Although a large amount of data are available on odor thresholds, experiments on the olfactory and trigeminal nervous systems show the two systems respond differently to sustained exposure. Vapor pressure correlated with human odor and pungency thresholds, but is not a measure of irritancy. A majority of human TLVs were based on limited experimental data, were intended to be occupational guidelines - not irritant thresholds - and were therefore not directly applicable for use in development of an irritancy scale.

Irritancy Database

The animal RD_{50} values were selected as the basis for development of a relative irritancy scale. Not only are animal RD_{50} data available for a large number of compounds, of the available data, RD_{50} directly measures the endpoint of interest, sensory irritation. The animal data have strong correlations with the human pungency threshold, by chemical class, and good correlations with human industrial guidelines, TLVs. Additionally, the animal data is controlled, follows a defined protocol, and is large. Finally, experimental evidence supports the hypothesis that animal data can be used to approximate the human pungency thresholds of individual VOCs. If human data were available, there would be no need to approximate potency. However, human pungency thresholds were available for only 5 CHBS VOCs (ethylacetate, butylacetate, 2-propanol, ethanol, 2-propanone). Although there are RD_{50} values available for a large number of VOCs, there are some VOCs found in indoor air for which we lack RD_{50} values. RD_{50}s for these missing compounds were estimated based on structure-activity relationships, specifically, the relationship between irritancy and vapor pressure for classes of VOCs.

An irritancy database of 148 VOCs was assembled (Appendix B). In addition to the VOCs of the CHBS data set, additional compounds from within the chemical classes of interest were included: alkane, aldehyde, ketone, ester, alkane, aromatic, alkene, chlorinated alkane, chlorinated aromatic, chlorinated alkene, terpene, and others. The irritancy database includes information on: identity (full name, chemical class, chemical abstract number, pseudonym(s)), RD_{50} (arithmetic mean and standard deviation), pungency

threshold, odor threshold (arithmetic mean and standard deviation), and saturated vapor pressure at physiological temperature (23° C). Using temperature and vapor pressure relationships, saturated vapor concentration was calculated at human physiological temperature, (23° C).

Interpolation of Missing Values for the CHBS Data

Missing RD_{50} values for VOCs from the CHBS data set were interpolated based upon the observed correlations by chemical class. The slope and intercept values were determined by linear regression analyses of the logarithms of available RD_{50} values versus log vapor pressure and versus log odor threshold by chemical class. Plots were also visually inspected for detection of outlier compounds. Secondary functional groups were considered when compounds were evaluated for inclusion/exclusion of VOCs in specific chemical classes. Reported in Table 25 are the slope and intercepts for the equations.

Table 26 presents RD_{50} concentrations for CHBS[1] VOCs. RD_{50} values were not available for compounds in several chemical classes: aromatic (6), alkane (9), chlorinated alkane (3), terpene (1), and chlorinated alkene (2). VP was used to interpolate missing RD_{50}s using slope and intercept values from Table 25. The largest proportion of the remainder of the missing RD_{50}s are from the less irritating chemical classes; i.e., the alkane or chlorinated alkane chemical class (12). RD_{50} concentrations for available alkanes are an

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1. Benzaldehyde and 1-phenylethanone are not included in further analyses as they are artifacts of sampling technique. See section "Indoor/Outdoor (I/O) Ratios" of Chapter 2.

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TABLE 25. Regression Slope and Intercept by Chemical Class

Equation	$RD_{50} = 10^{(m\log(VP) + b)}$		$RD_{50} = 10^{\left(m\log\left(O_T\right) + b\right)}$		$O_T = 10^{(m\log(VP) + b)}$	
Slope & Intercept [a][b]	m	b	m	b	m	b
Alcohol	0.87****	0.11	0.52*	3.3****	1.4****	-5.1****
Aldehyde	NA	NA	NA	NA	0.45*	-2.3*
Ketone	1.4*	-2.4	0.63*	3.4****	1.1***	-4.2***
Ester	NA	NA	NA	NA	1.5***	-6.7***
Alkane	NA	NA	NA	NA	0.65***	-2.1**
Aromatic	0.54	1.27	NA	NA	0.82*	-3.4*
Alkene	NA	NA	NA	NA	1.9*	-13*
Chlorinated Alkane	NA	NA	NA	NA	0.73*	-3.1*

a. Significance level:
* - $p < 0.05$.
** - $p < 0.01$.
*** - $p < 0.001$.
**** - $p < 0.0001$.

b. NA indicates insufficient compounds available for regression.

order of magnitude higher than RD_{50} concentrations from more irritating classes (ester, aromatic, aldehyde); therefore, missing RD_{50}s from the alkane class are less important in terms of an ordered relative irritancy scale. Data were also missing for the terpene and chlorinated alkene chemical classes; however, only 3 RD_{50} values were missing and could not be estimated (limonene, tetrachloroethylene, trichloroethene).

Irritancy Scale

Using relationships among the various measures, a single, consistent irritancy scale was developed. The goal was to develop an ordered, relative irritancy scale to reflect the

TABLE 26. RD_{50} (ppm) for CHBS VOCs

Compound	Chemical Class	RD_{50} (ppm)[a]
Benzene	Aromatic	9.74E+3[b]
2-Butoxyethanol	Alcohol	2.83E+03
n-Butyl acetate	Ester	7.33E+02
n-Decane	Alkane	NA
Dichloromethane	Chlorinated Alkane	NA
n-Dodecane	Alkane	NA
Ethanol	Alcohol	2.73E+04
Ethyl acetate	Ester	5.97E+02
Ethylbenzene	Aromatic	2.75E+03
2-Ethyltoluene	Aromatic	1.434E+3[c]
3,4-Ethyltoluene	Aromatic	1.55E+3[d]
n-Heptane	Alkane	1.74E+04
n-Hexanal	Aldehyde	1.12E+03
n-Hexane	Alkane	NA
Limonene	Terpene	NA
Methylcyclohexane	Alkane	NA
Methylcyclopentane	Alkane	NA
3-Methylhexane	Alkane	NA
n-Nonane	Alkane	6.22E+04
n-Octane	Alkane	1.82E+04
n-Pentanal	Aldehyde	1.16E+03
n-Pentane	Alkane	NA
2-Propanol	Alcohol	1.13E+04
2-Propanone	Ketone	5.05E+04
Styrene	Aromatic	5.74E+02
Tetrachloroethylene	Chlorinated Alkene	NA
Toluene	Aromatic	4.52E+03
1,1,1-Trichloroethane	Chlorinated Alkane	NA
Trichloroethene	Chlorinated Alkene	NA
Trichlorofluoromethane	Chlorinated Alkane	NA
1,2,3-Trimethylbenzene	Aromatic	1.11E+3[e]
1,2,4-Trimethylbenzene	Aromatic	1.25E+3[f]
1,3,5-Trimethylbenzene	Aromatic	1.430E+3[g]
2,2,5-Trimethylhexane	Alkane	NA
n-Undecane	Alkane	NA
m,p-Xylene	Aromatic	1.33E+03
o-Xylene	Aromatic	1.47E+03

a. NA indicates RD_{50} concentration was not available and could not be estimated.

b. $RD_{50} = 10^{(0.54\log (1.13E+5) + 1.27)}$

c. $RD_{50} = 10^{(0.54\log (3.19E+3) + 1.27)}$

d. $RD_{50} = 10^{(0.54\log (3.67E+3) + 1.27)}$

e. $RD_{50} = 10^{(0.54\log (1.98E+3) + 1.27)}$

f. $RD_{50} = 10^{(0.54\log (2.49E+3) + 1.27)}$

g. $RD_{50} = 10^{(0.54\log (3.18E+3) + 1.27)}$

irritant nature of the individual CHBS VOCs. Observed CHBS VOC concentrations were relatively low. Low concentration levels affected the analysis in two different ways.

First, low values allowed an important assumption to be made, that irritant stimulus receptors were unlikely to be saturated, and therefore total irritant potency was equivalent to the sum of the individual VOC potencies. A VOC metric for irritancy was based on the sum of the irritancies of individual compounds.

Second, not only were concentrations low, geometric means of observed concentrations for the CHBS VOCs were well below reported odor thresholds. One approach to development of a VOC metric based on odor would be to use the compounds that dominate the odor of the mixture. Such a metric might be useful for symptom prediction in a different set of office buildings; however, as observed concentrations in the California buildings were below O_Ts, no compound was likely to have been very odorous. Therefore, a simple VOC metric using the odor threshold data, based on the sum of odor-weighted compounds, was investigated.

Reference Compound

To compare relative irritancies across compounds, individual VOCs are normalized to a selected reference compound. Toluene was chosen to be the reference compound based on the following standards. 1) Data existed for three physiological measures: human odor threshold (O_T), animal irritancy (RD_{50}), and human pungency threshold (P_T). 2) Internal consistency was observed across the three measures, specifically, $P_T =\sim RD_{50} >>> O_T$;

these relative relationships were observed for most of the compounds studied. 3) For practical purposes, the reference compound was chosen to be roughly in the middle of the scale for VP. 4) The reference compound (toluene) is almost always found in buildings (Berglund et al., 1986). 5) Analysis and sampling methods were also considered. The compound 2-propanol also fulfills the prior standards, but was not chosen as the reference VOC because the compound's breakthrough volume on the Tenax sampler is smaller than that for toluene. Thus, toluene measurements are more assured.

The values are referenced to toluene using the following:

$$Relative\ Irritancy\ (VOC_i)\ =\ \frac{RD_{50}\ (Toluene)}{RD_{50}\ (VOC_i)} \qquad \text{(EQ 2)}$$

where:
$i =$ individual VOC.

Ordering

The CHBS VOCs were then ordered according to irritancy *relative* to toluene. The relative scale will expand or contract dependent upon the actual VOCs sampled in the field; however, a somewhat different mixture of VOCs will retain the same relative order for this set of VOCs as that found for the CHBS data set. The strength of this technique is that the focus is on those compounds present that demonstrate the greatest relative potential to be irritating.

Table 27 presents CHBS VOCs ordered by their relative irritancy, referenced to toluene. For the CHBS VOCs, the most irritating compounds were in the aromatic, ester and

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TABLE 27. Ordered relative irritancy scale for the CHBS VOCs

Compound	Chemical Class	Relative Irritancy Referenced to Toluene	RD_{50} (ppm)[a]
Styrene	Aromatic	7.9	5.74E+2
Ethylacetate	Ester	7.6	5.97E+2
n-Butyl acetate	Ester	6.2	7.33E+2
1,2,3-Trimethylbenzene	Aromatic	4.1	1.11E+3[a]
n-Hexanal	Aldehyde	4.0	1.12E+3
n-Pentanal	Aldehyde	3.9	1.16E+3
1,2,4-Trimethylbenzene	Aromatic	3.6	1.25E+3[a]
m/p-Xylene	Aromatic	3.4	1.33E+3
1,3,5-Trimethylbenzene	Aromatic	3.16	1.430E+3[a]
2-Ethyltoluene	Aromatic	3.15	1.434E+3[a]
o-Xylene	Aromatic	3.08	1.47E+3
3/4-Ethyltoluene	Aromatic	2.9	1.55E+3[a]
Ethylbenzene	Aromatic	1.7	2.75E+3
2-Butoxyethanol	Alcohol	1.6	2.82E+3
Toluene	Aromatic	1 (reference)	4.52E+3
Benzene	Aromatic	0.46	9.74E+3[a]
2-Propanol	Aromatic	0.40	1.13E+4
n-Heptane	Alkane	0.26	1.74E+4
n-Octane	Alkane	0.25	1.82E+4
Ethanol	Alcohol	0.17	2.73E+4
2-Propanone	Ketone	0.09	5.05E+4
n-Nonane	Alkane	0.07	6.22E+4

a. RD_{50} value estimated using vapor pressure.

aldehyde chemical classes. Styrene is the most irritating compound, followed by ethylacetate, *n*-butylacetate, 1,2,3-trimethylbenzene, and *n*-hexanal. Less irritating compounds are in the alkane, alcohol and ketone chemical classes (ethanol, 2-propanone (acetone), and *n*-nonane). The low relative irritancy of two bioeffluents (ethanol and acetone) is plausible biologically; human beings have adapted to low levels of bioeffluents

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over an evolutionary time scale. Although this ordering scheme is based on a limited number of chemical classes, the finding that the alkanes (*n*-heptane, *n*-octane, *n*-nonane) are below toluene on the relative irritancy scale supports the earlier assumption that lack of RD_{50} data for the alkane chemical class was less important in terms of identification of the most irritating CHBS VOCs[1].

As measured by RD_{50}s, the range of irritancies for the CHBS VOCs was large and spanned roughly 2 orders of magnitude (570 - 62,000 ppm). More specifically, the reference compound (toluene) marks an important division between relative irritancies. RD_{50}s are fairly similar in magnitude for compounds more irritating than toluene; however, RD_{50}s increase rapidly for compounds below the reference compound. RD_{50}s increase almost 4000 ppm from styrene to toluene (570 - 4,500 ppm, respectively). However, RD_{50}s increase 5000 ppm from toluene to benzene (4,500 - 9,700 ppm, respectively); i.e., RD_{50}s increase more between the reference compound and the next least irritating compound than for the first 15 compounds of the relative irritancy scale. Finally, RD_{50}s increase more than 6-fold from benzene to *n*-nonane (9,700 - 62,000 ppm, respectively). These observations support the approach used here that targets irritating compounds. That is, especially in comparison with the most irritating compounds, the least irritating compounds are effectively not irritating; thus, the least irritating compounds are very unlikely to be useful in a metric based on irritancy. Therefore, exclusion of these non-irritating compounds from the new metric was warranted.

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1. However, in cases with many alkanes at high levels, information on their irritancy could be more important to obtain.

Conclusions

An integrated, relative irritancy scale for VOCs commonly found indoors has been developed. The irritancy scale is based on the animal bioassay of sensory irritation, RD_{50}. Missing RD_{50} values for specific VOCs were estimated based on relationships with vapor pressure by chemical class. The irritancy scale ranged over 2 orders of magnitude. The most irritating compounds were in the aromatic, ester and aldehyde chemical classes. The 5 most irritating compounds were styrene, ethylacetate, *n*-butylacetate, 1,2,3-trimethylbenzene, and *n*-hexanal. The 5 least irritating compounds (*n*-heptane, *n*-octane, ethanol, 2-propanone (acetone), *n*-nonane) were in the alkane, alcohol and ketone chemical classes.

The general approach described herein can be used in other settings for the development of an irritancy scale. However, as the irritancy scale developed for the CHBS data set is relative to toluene, the relative ordering of these compounds will remain the same in other settings, although the scale may expand and/or contract dependent upon compounds. Therefore, the relative irritancy scale can be used broadly for investigations of the indoor environment. The utility in symptom prediction of a VOC metric based on the integrated, relative irritant scale developed for CHBS VOCs is explored in detail in the following chapter.

Appendices

**Pungency and Odor Threshold (log ppm) by Vapor Pressure (log ppm):
Alcohols, Ketones, Esters**

Presented in Figure 12 to Figure 14 are plots of saturated vapor pressure with human

pungency and human odor thresholds, by alcohol, ketone and ester chemical classes.

Pungency threshold data were reported by Cometto-Muniz and Cain (1993). Odor

threshold data were reported by Devos et al. (1990). Using temperature and vapor pressure

relationships, saturated vapor concentration was calculated at human physiological

temperature, (23°C).
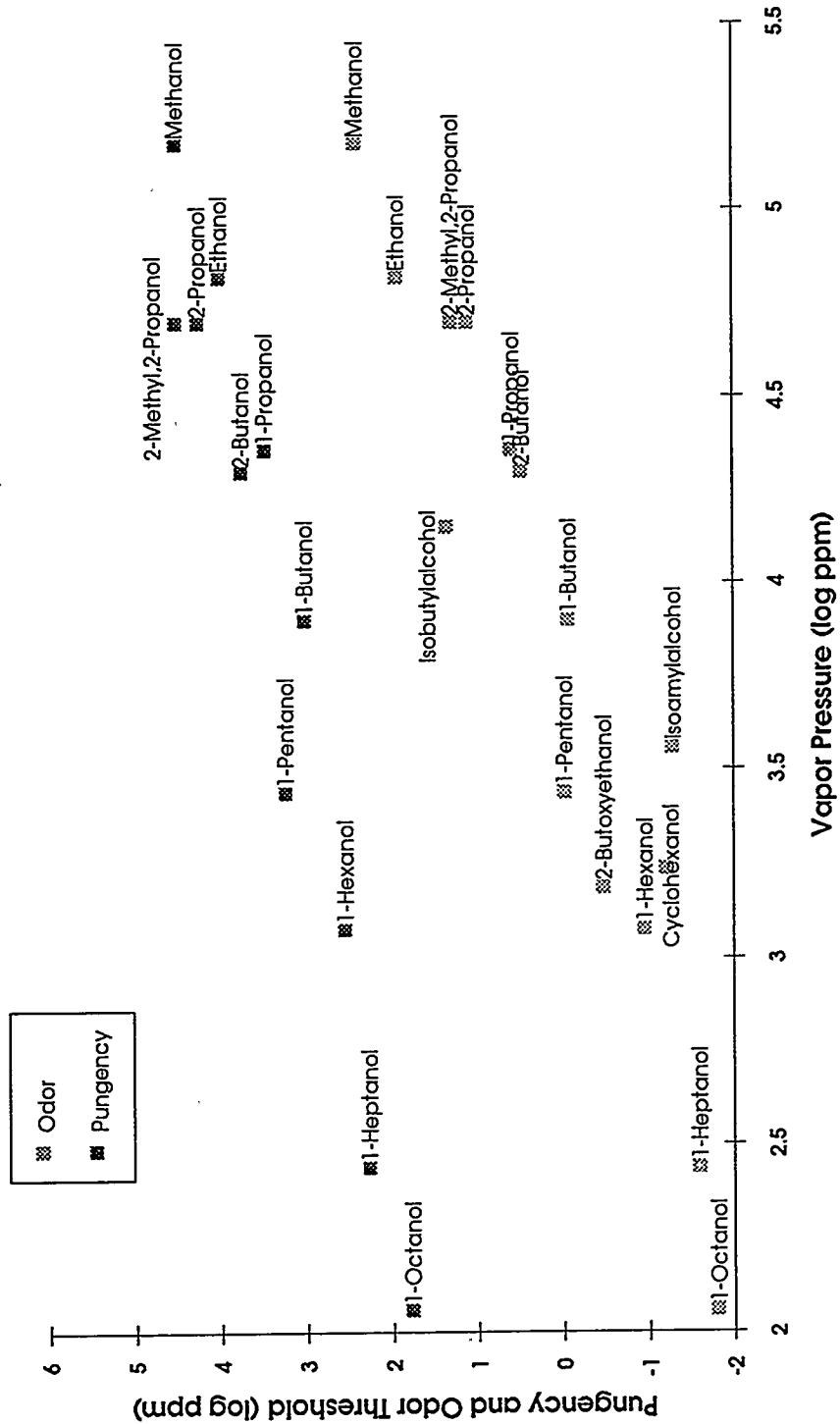
FIGURE 12. Alcohols: Pungency and Odor Thresholds (log ppm) by Vapor Pressure (log ppm)

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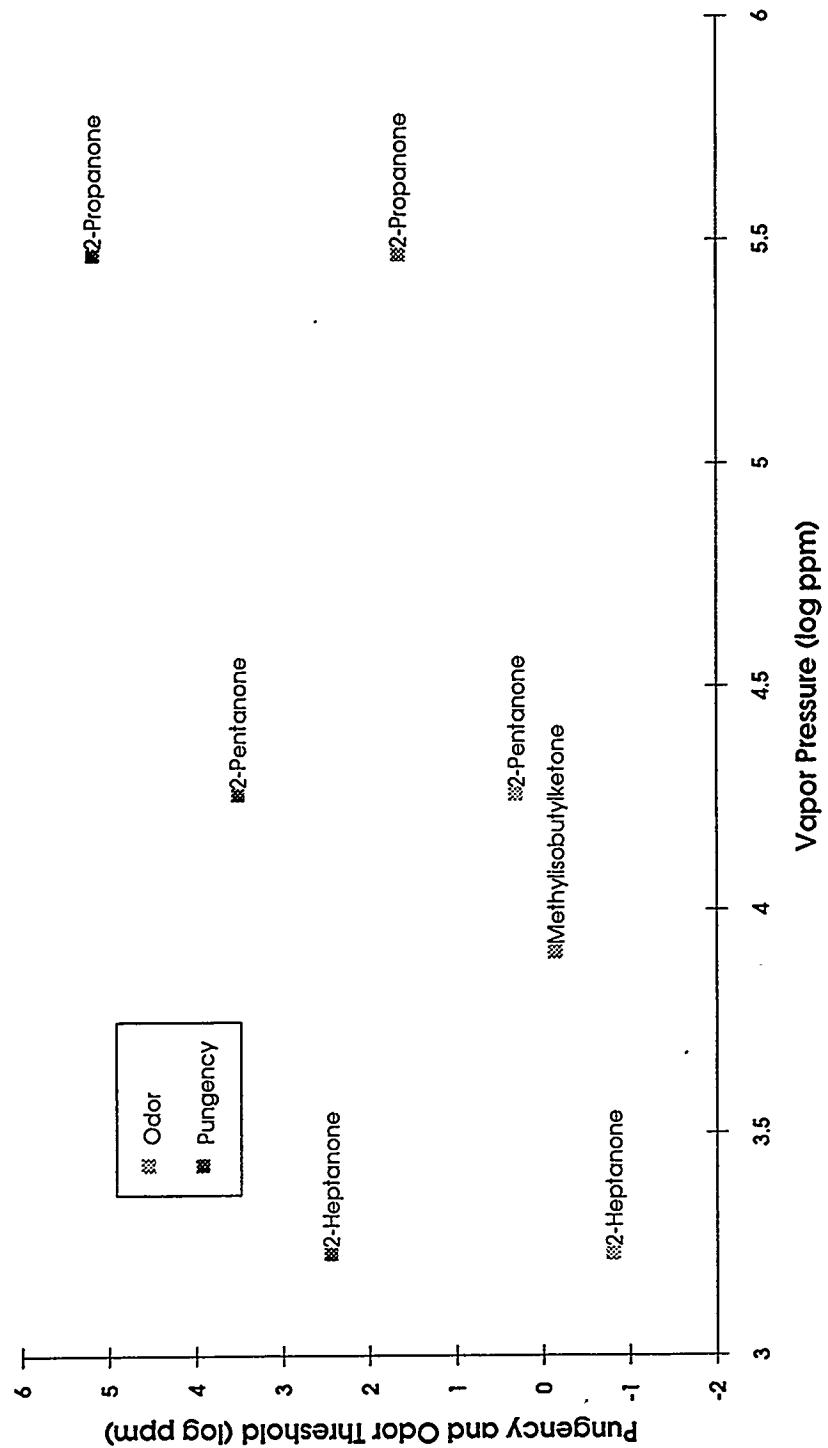
FIGURE 13. Ketones: Pungency and Odor Thresholds (log ppm) by Vapor Pressure (log ppm)
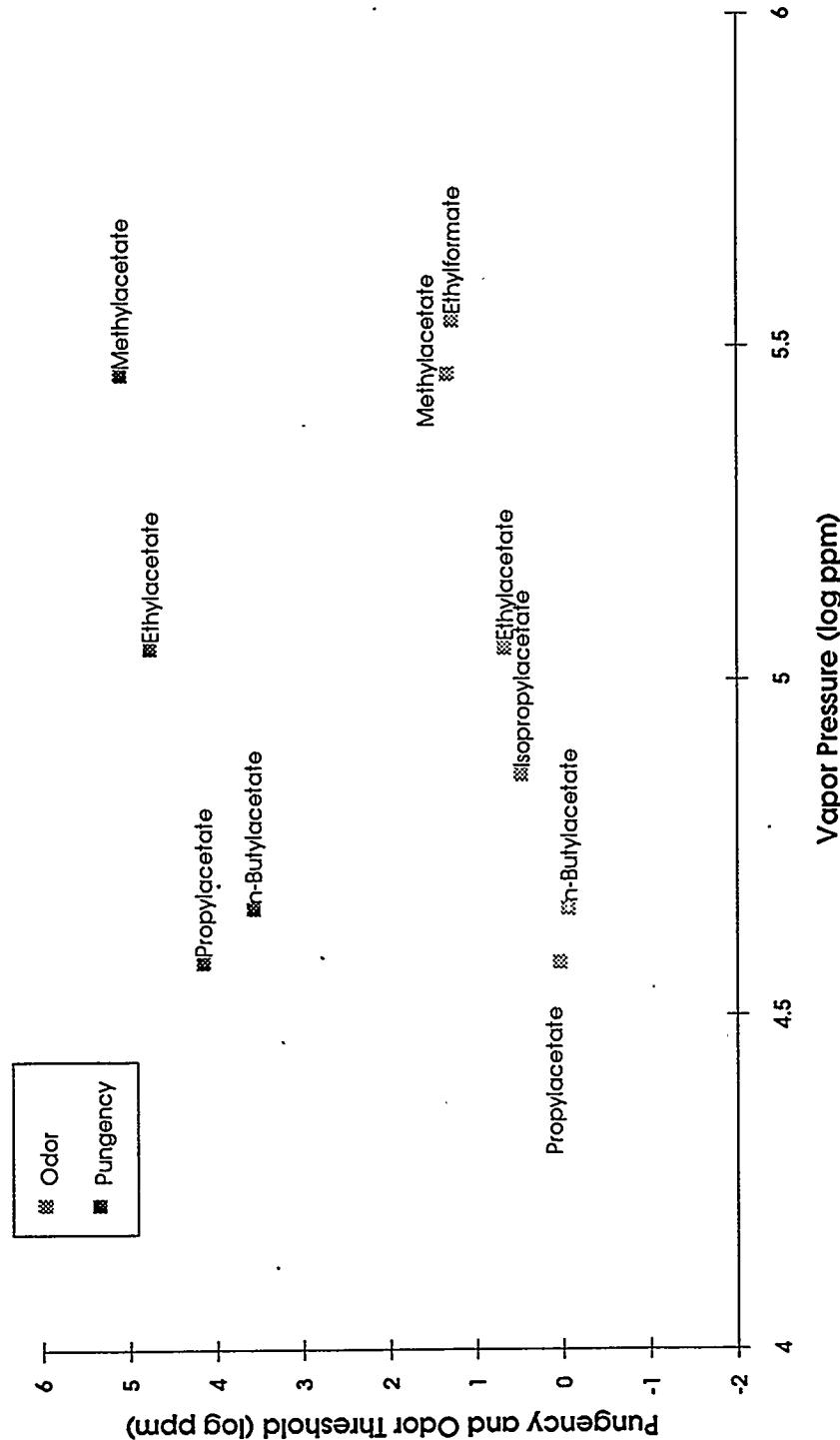
FIGURE 14. Esters: Pungency and Odor Thresholds (log ppm) by Vapor Pressure (log ppm)

Appendix C Irritancy Database

TABLE 28. Irritancy Database I : Compound, Chemical Class[a], CHBS VOC[b], RD$_{50}$ (ppm)[c], RD$_{50}$ Standard Deviation (ppm), RD$_{50}$ Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD$_{50}$ (ppm)	RD$_{50}$ St. Dev. (ppm)	RD$_{50}$ Reference	PT (ppm)
Acetaldehyde	Aldehyde	no	3.43E+03	1.01E+03	(Kane et al., 1980; Steinhagen and Barrow, 1984; Babiuk et al., 1985)	NA
Acetic acid	Carbxacid	no	3.70E+02	2.93E+02	(Kane et al., 1980; Schaper, 1993)	NA
Acetonitrile	Nitrile	no	NA	NA	NA	NA
Acrolein	Aldehyde	no	2.48E+00	1.69E+00	(Kane and Alarie, 1977; Nielsen et al., 1984; Steinhagen and Barrow, 1984; Babiuk et al., 1985; Schaper, 1993)	NA
Allyl acetate	Allyl	no	2.70E+00	2.83E-01	(Nielsen et al., 1984; Schaper, 1993)	NA
Allyl alcohol	Allyl	no	2.67E+00	1.16E+00	(Nielsen et al., 1984; Schaper, 1993)	NA
Allyl chloride	Allyl	no	2.04E+03	4.17E+02	(Nielsen and Bakbo, 1985; Danish National Institute of Occupational Health, 1989)	NA
Allyl ether	Allyl	no	5.00E+00	NA	(Nielsen et al., 1984)	NA
Amylbenzene(n-)	Aromatic	no	2.85E+02	7.78E+01	(Nielsen and Alarie, 1982; Danish National Institute of Occupational Health, 1989)	NA
Benzaldehyde	Aldehyde	yes	3.64E+02	4.31E+01	(Steinhagen and Barrow, 1984)	NA
Benzene	Aromatic	yes	NA	NA	NA	NA
Benzylchloride	ChloAro	no	2.20E+01	7.07E+00	(Kane et al., 1980; Schaper, 1993)	NA
Biphenyl	Aromatic	no	NA	NA		NA
Butadiene(1,3-)	Diene	no	NA	NA	NA	NA
Butanal	Aldehyde	no	1.02E+03	NA	(Danish National Institute of Occupational Health, 1989)	NA
Butanol(1-)	Alcohol	no	4.38E+03	2.92E+03	(Kane et al., 1980; DeCeaurriz et al., 1981; Schaper, 1993)	1.05E+03
Butanol(2-)	Alcohol	no	NA	NA	NA	5.62E+03

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TABLE 28. Irritancy Database I (Continued): Compound, Chemical Class[a], CHBS VOC[b], RD50 (ppm)[c], RD50 Standard Deviation (ppm), RD50 Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD50 (ppm)	RD50 St. Dev. (ppm)	RD50 Reference	PT (ppm)
Butenal(2-)	Aldehyde	no	3.50E+00	NA	(Danish National Institute of Occupational Health, 1989)	NA
Butene(1-)	Alkene	no	7.78E+00	NA	(Kane and Alarie, 1978)	NA
Butene(cis-2-)	Alkene	no	1.07E+01	NA	(Kane and Alarie, 1978)	NA
Butoxy ethanol(2-)	Alcohol	yes	2.83E+03	NA	(Kane et al., 1980)	NA
Butyl acetate(n-)	Ester	yes	7.33E+02	3.54E+00	(Schaper, 1993)	3.72E+03
Butyl acetate(sec-)	Ester	no	NA	NA	NA	5.62E+02
Butyl acetate(tert-)	Ester	no	1.60E+04	NA	(Schaper, 1993)	1.78E+03
Butylamine(n-)	Amine	no	2.19E+02	7.50E+01	(Nielsen and Vinggaard, 1988; Gagnaire et al., 1989; Schaper, 1993)	NA
Butylbenzene(n-)	Aromatic	no	7.10E+02	NA	(Nielsen and Alarie, 1982)	NA
Butylbenzene(tert-)	Aromatic	no	7.60E+02	NA	(Nielsen and Alarie, 1982)	NA
Butyltoluene(p-tert-)	Aromatic	no	3.60E+02	NA	(Nielsen and Alarie, 1982)	NA
Chlorobenzene	ChloAro	no	1.05E+03	NA	(DeCeaurriz et al., 1981)	NA
Chloroform	ChloHC	no	NA	NA	NA	NA
Chlororacetophe-none(alpha-)	Ketone	no	9.60E-01	NA	(Alarie, 1981)	NA
Cyclohexane	Alkane	no	NA	NA	NA	NA
Cyclohexanol	Alcohol	no	NA	NA	NA	NA
Cyclohexanone	Ketone	no	7.56E+02	NA	(DeCeaurriz et al., 1981)	NA
Decane(n-)	Alkane	yes	NA	NA	NA	NA
Decyl acetate	Ester	no	NA	NA	NA	4.17E+00
Dichlorobenzene(o-)	ChloAro	no	1.82E+02	7.07E-01	(DeCeaurriz et al., 1981; Schaper, 1993)	NA
Dichlorobenzene(p-)	ChloAro	no	1.82E+02	NA	(Danish National Institute of Occupational Health, 1989)	NA
Dichloromethane	ChloHC	yes	NA	NA	NA	NA
Diethylamine	Amine	no	1.93E+02	1.27E+01	(Gagnaire et al., 1989; Nielsen and Yamagiwa, 1989)	NA

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TABLE 28. Irritancy Database I (Continued): Compound, Chemical Class[a], CHBS VOC[b], RD$_{50}$ (ppm)[c], RD$_{50}$ Standard Deviation (ppm), RD$_{50}$ Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD$_{50}$ (ppm)	RD$_{50}$ St. Dev. (ppm)	RD$_{50}$ Reference	P$_T$ (ppm)
Diisobutyl ketone	Ketone	no	2.87E+02	NA	(Danish National Institute of Occupational Health, 1989)	NA
Diisopropylamine	Amine	no	1.61E+02	NA	(Gagnaire et al., 1989)	NA
Dimethylamine	Amine	no	3.85E+02	2.74E+02	(Steinhagen et al., 1982; Gagnaire et al., 1989)	NA
Dioxane(1,4-)	Ether	no	NA	NA	NA	NA
Dipropylene glycol methyl ether	Ether	no	NA	NA	NA	NA
Dodecane(n-)	Alkane	yes	NA	NA	NA	NA
Dodecyl acetate	Ester	no	NA	NA	NA	1.55E+00
Ethanol	Alcohol	yes	2.73E+04	NA	(Alarie, 1981)	1.00E+04
Ethanolamine	Amine	no	NA	NA	NA	NA
Ethoxyethanol(2-)	Alcohol	no	NA	NA	NA	NA
Ethyl acetate	Ester	yes	5.97E+02	2.40E+01	(Kane et al., 1980; DeCeaurriz et al., 1981)	5.75E+04
Ethyl acrylate	Acrylate	no	3.15E+02	NA	(DeCeaurriz et al., 1981)	NA
Ethylamine	Amine	no	1.51E+02	NA	(Gagnaire et al., 1989)	NA
Ethyl amyl ketone	Ketone	no	NA	NA	NA	NA
Ethylbenzene	Aromatic	yes	2.75E+03	1.86E+03	(Kane et al., 1980; Nielsen and Alarie, 1982)	NA
Ethylbutanal(2-)	Aldehyde	no	8.43E+02	NA	(Danish National Institute of Occupational Health, 1989)	NA
Ethylene	Alkene	no	1.49E+01	NA	(Kane and Alarie, 1978)	NA
Ethylenediamine	Amine	no	NA	NA	NA	NA
Ethylenimine	Amine	no	NA	NA	NA	NA
Ethyl ether	Ether	no	NA	NA	NA	NA
Ethyl formate	Ester	no	NA	NA	NA	NA
Ethyltoluene(2-)	Aromatic	yes	NA	NA	NA	NA
Ethyltoluene(3/4-)	Aromatic	yes	NA	NA	NA	NA

TABLE 28. Irritancy Database I (Continued): Compound, Chemical Class[a], CHBS VOC[b], RD50 (ppm)[c], RD50 Standard Deviation (ppm), RD50 Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD50 (ppm)	RD50 St. Dev. (ppm)	RD50 Reference	PT (ppm)
Formaldehyde	Aldehyde	no	1.03E+01	1.12E+01	(Kane and Alarie, 1977; Alarie, 1981; Chang et al., 1981; DeCeaurriz et al., 1981; Chang and Barrow, 1984; Schaper, 1993)	NA
Formic acid	Carbxacid	no	NA	NA	NA	NA
Furfural	Aldehyde	no	2.87E+02	NA	(Danish National Institute of Occupational Health, 1989)	NA
Heptane(n-)	Alkane	yes	1.74E+04	NA	(Kristiansen and Nielsen, 1988)	NA
Heptanol(1-)	Alcohol	no	NA	NA	NA	1.90E+02
Heptanol(4-)	Alcohol	no	NA	NA	NA	3.23E+02
Heptanone(2-)	Ketone	no	8.93E+02	NA	(Schaper, 1993)	2.81E+02
Heptyl acetate	Ester	no	NA	NA	NA	3.16E+02
Heptylamine(n-)	Amine	no	3.60E+01	NA	(Nielsen and Vinggaard, 1988)	NA
Hexanal(n-)	Aldehyde	yes	1.12E+03	NA	(Danish National Institute of Occupational Health, 1989)	NA
Hexane(n-)	Alkane	yes	NA	NA	NA	NA
Hexanol(1-)	Alcohol	no	2.39E+02	NA	(Schaper, 1993)	3.55E+02
Hexyl acetate(n-)	Ester	no	7.40E+02	NA	(Schaper, 1993)	5.62E+02
Hexyl acetate(sec-)	Ester	no	NA	NA	NA	NA
Hexylamine(n-)	Amine	no	6.60E+01	NA	(Nielsen and Vinggaard, 1988)	NA
Hexylbenzene(n-)	Aromatic	no	1.25E+02	NA	(Nielsen and Alarie, 1982)	NA
Isoamyl alcohol	Alcohol	no	2.59E+03	2.63E+03	(Kane et al., 1980; Schaper, 1993)	NA
Isobutyl alcohol	Alcohol	no	1.82E+03	NA	(DeCeaurriz et al., 1981)	NA
Isobutyraldhyde	Aldehyde	no	3.59E+03	8.14E+02	(Steinhagen and Barrow, 1984)	NA
Isopropyl acetate	Ester	no	4.26E+03	NA	(Schaper, 1993)	NA
Isopropylamine	Amine	no	1.57E+02	NA	(Gagnaire et al., 1989)	NA
Isopropyl ether	Ether	no	NA	NA	NA	NA
Limonene	Terpene	yes	NA	NA	NA	NA

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TABLE 28. Irritancy Database I (Continued): Compound, Chemical Class[a], CHBS VOC[b], RD_{50} (ppm)[c], RD_{50} Standard Deviation (ppm), RD_{50} Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD_{50} (ppm)	RD_{50} St. Dev. (ppm)	RD_{50} Reference	P_T (ppm)
Menthol	Terpene	no	4.50E+01	NA	(Schaper, 1993)	NA
Methanol	Alcohol	no	3.34E+04	1.15E+04	(Kane et al., 1980; Schaper, 1993)	3.24E+04
Methyl-2-Propanol(2-)	Alcohol	no	NA	NA	NA	3.24E+04
Methyl-5-hexan-2-one	Ketone	no	1.23E+03	NA	(Schaper, 1993)	NA
Methyl acetate	Ester	no	8.29E+02	NA	(Schaper, 1993)	1.26E+05
Methyl acrylate	Acrylate	no	NA	NA	NA	NA
Methylamine	Amine	no	1.41E+02	NA	(Gagnaire et al., 1989)	NA
Methylbutanal(3-)	Aldehyde	no	1.01E+03	NA	(Danish National Institute of Occupational Health, 1989)	NA
Methyl chloride	ChloHC	no	NA	NA	NA	NA
Methylcyclohexane	Alkane	yes	NA	NA	NA	NA
Methylcyclohexanol	Alcohol	no	NA	NA	NA	NA
Methylcyclopentane	Alkane	yes	NA	NA	NA	NA
Methyl ethyl ketone	Ketone	no	1.71E+04	1.25E+04	(DeCeaurriz et al., 1981; Hansen et al., 1992; Schaper, 1993)	NA
Methylhexane(3-)	Alkane	yes	NA	NA	NA	NA
Methyl isobutyl ketone	Ketone	no	3.20E+03	NA	(DeCeaurriz et al., 1981)	NA
Methyl methacrylate	Acrylate	no	NA	NA	NA	NA
Methylstyrene(alpha-)	Allyl	no	2.73E+02	NA	(Schaper, 1993)	NA
Naphtalene	ChloHC	no	NA	NA	NA	NA
Nitrobenzene	Aromatic	no	NA	NA	NA	NA
Nonane(n-)	Alkane	yes	6.22E+04	NA	(Kristiansen and Nielsen, 1988)	NA
Octanal	Aldehyde	no	NA	NA	NA	NA
Octane(n-)	Alkane	yes	1.82E+04	NA	(Kristiansen and Nielsen, 1988)	NA
Octanol(1-)	Alcohol	no	4.72E+01	NA	(Schaper, 1993)	6.03E+01
Octyl acetate	Ester	no	NA	NA	NA	6.31E+02
Pentanal(n-)	Aldehyde	yes	1.16E+03	4.88E+01	(Steinhagen and Barrow, 1984)	NA

TABLE 28. Irritancy Database I (Continued): Compound, Chemical Class[a], CHBS VOC[b], RD50 (ppm)[c], RD50 Standard Deviation (ppm), RD50 Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD50 (ppm)	RD50 St. Dev. (ppm)	RD50 Reference	PT (ppm)
Pentane(n-)	Alkane	yes	NA	NA	NA	NA
Pentanol(1-)	Alcohol	no	2.32E+03	2.43E+03	(Kane et al., 1980; Schaper, 1993)	3.24E+00
Pentanol(iso-)	Alcohol	no	4.45E+03	NA	(Alarie, 1981)	NA
Pentanone(2-)	Ketone	no	5.93E+03	NA	(Schaper, 1993)	1.74E+03
Pentyl acetate	Ester	no	1.53E+03	NA	(Alarie, 1981)	1.41E+03
Pentylamine(n-)	Amine	no	1.28E+02	NA	(Nielsen and Vinggaard, 1988)	NA
Phenol	Phenol	no	1.66E+02	NA	(DeCeauriz et al., 1981)	NA
Phenylethanone(1-)	Ketone	yes	NA	NA	NA	NA
Propanal(n-)	Aldehyde	no	2.75E+03	NA	(Alarie, 1981)	NA
Propanol(1-)	Alcohol	no	1.27E+04	NA	(Alarie, 1981)	3.02E+03
Propanol(2-)	Alcohol	yes	1.13E+04	8.98E+03	(Kane et al., 1980; DeCeauriz et al., 1981)	1.78E+04
Propanone(2-)	Ketone	yes	5.05E+04	3.82E+04	(Kane et al., 1980; DeCeauriz et al., 1981)	1.51E+05
Propyl acetate	Ester	no	7.93E+02	NA	(Schaper, 1993)	1.41E+04
Propylamine(n-)	Amine	no	2.66E+02	1.58E+02	(Nielsen and Vinggaard, 1988; Gagnaire et al., 1989)	NA
Propylbenzene	Aromatic	no	2.31E+03	1.10E+03	(Nielsen and Alarie, 1982; Danish National Institute of Occupational Health, 1989)	NA
Propylene	Alkene	no	1.50E+00	NA	(Kane and Alarie, 1978)	NA
Propylene glycol monomethyl ether	Ether	no	NA	NA	NA	NA
Styrene	Aromatic	yes	5.74E+02	4.12E+02	(DeCeauriz et al., 1981; Schaper, 1993)	NA
Tetrachloroethane(1,1,2,2-)	ChloHC	no	NA	NA	NA	NA
Tetrachloroethylene	ChloAlk	yes	NA	NA	NA	NA
Toluene	Aromatic	yes	4.52E+03	1.02E+03	(Kane et al., 1980; Nielsen and Alarie, 1982; Schaper, 1993)	NA

TABLE 28. Irritancy Database I (Continued): Compound, Chemical Class[a], CHBS VOC[b], RD_{50} (ppm)[c], RD_{50} Standard Deviation (ppm), RD_{50} Reference, Pungency Threshold (ppm)[d],

Compound	Chemical Class	CHBS VOC	RD_{50} (ppm)	RD_{50} St. Dev. (ppm)	RD_{50} Reference	P_T (ppm)
Toluene 2,4-diisocyanate	IsoCyan	no	3.40E-01	2.00E-01	(Barrow et al., 1978; Sangha and Alarie, 1979; DeCeaurriz et al., 1981; Schaper, 1993)	NA
Trichlorobenzene(1,2,4-)	ChloAro	no	NA	NA	NA	NA
Trichloroethane(1,1,1-)	ChloHC	yes	NA	NA	NA	NA
Trichloroethylene	ChloAlk	yes	NA	NA	NA	NA
Trichlorofluoromethane	ChloHC	yes	NA	NA	NA	NA
Trichloropropane(1,2,3-)	ChloHC	no	NA	NA	NA	NA
Triethylamine	Amine	no	1.71E+02	2.12E+01	(Gagnaire et al., 1989; Nielsen and Yamagiwa, 1989)	NA
Trimethylbenzene(1,2,3-)	Aromatic	yes	NA	NA	NA	NA
Trimethylbenzene(1,2,4-)	Aromatic	yes	NA	NA	NA	NA
Trimethylbenzene(1,3,5-)	Aromatic	yes	NA	NA	NA	NA
Trimethylhexane(2,2,5-)	Alkane	yes	NA	NA	NA	NA
Undecane(n-)	Alkane	yes	NA	NA	NA	NA
Xylene(m,p-)	Aromatic	yes	1.33E+03	NA	NA	NA
Xylene(o-)	Aromatic	yes	1.47E+03	NA	(DeCeaurriz et al., 1981)	NA

a. NA (not applicable) indicates information not available. Carbxacid = Carboxylic Acid; ChloAlk = Chlorinated Alkene; ChloHC = Chlorinated hydrocarbons; IsoCyan = Iso Cyanate.

b. Whether VOC was sampled in the California Healthy Building Study (y = Yes; n = No).

c. RD_{50}(ppm) averaged from available values; references given in sixth column.

d. All pungency thresholds (ppm) from Figure 1 (Cometto-Muniz and Cain, 1993).

TABLE 29. Irritancy Database II : Compound, Chemical Abstract Number[a], Odor Threshold (ppm)[b], Odor Threshold Standard Deviation (ppm), Vapor Pressure (ppm)[c], Pseudonym

Compound	Chemical Abstract Number	O_T (ppm)	O_T Std. Dev. (ppm)	Vapor Pressure (ppm)	Pseudonym
Acetaldehyde	00075-07-0	6.37E-01	7.73E-01	1.48E+06	Ethanal, Acetic aldehyde, Ethyl aldehyde
Acetic acid	00064-19-7	6.42E-01	8.79E-01	1.81E+04	NA
Acetonitrile	00075-05-8	1.02E+02	4.20E+01	1.10E+05	Ethanenitrile
Acrolein	00107-02-8	2.94E-01	3.64E-01	3.95E+05	2-Propenal
Allyl acetate	00591-87-7	NA	NA	NA	NA
Allyl alcohol	00107-18-6	4.96E-01	4.52E-01	2.87E+04	2-Propen-1-ol
Allyl chloride	00107-05-1	4.79E-01	NA	5.36E+05	3-Chloropropene
Allyl ether	00557-40-4	NA	NA	NA	1-Propene, 3,3'-oxybis
Amylbenzene(n-)	00538-68-1	NA	NA	NA	NA
Benzaldehyde	00100-52-7	5.86E-02	3.93E-02	1.06E+03	NA
Benzene	00071-43-2	4.73E+00	3.11E+00	1.13E+05	NA
Benzylchloride	00100-44-7	3.59E-02	1.53E-02	1.42E+03	alpha-chlorotoluene
Biphenyl	00092-52-4	NA	NA	6.05E+01	NA
Butadiene(1,3-)	00106-99-0	1.44E+00	3.96E-01	4.04E+06	NA
Butanal	00123-72-8	1.15E-02	7.80E-03	NA	Butyraldehyde
Butanol(1-)	00071-36-3	8.50E-01	1.21E+00	8.03E+03	n-Butanol, n-Butyl Alcohol
Butanol(2-)	00078-92-2	2.96E+00	3.05E+00	1.99E+04	NA
Butenal(2-)	00123-73-9	1.47E-01	6.82E-02	NA	trans-2-Butenal, crotonaldehyde
Butene(1-)	00106-98-9	5.76E-01	2.88E-01	4.28E+06	alpha-Butylene, ethylethylene
Butene(cis-2-)	00107-01-7	2.19E-01	NA	3.32E+06	Pseudo-butylene, sym-dimethylethylene, beta-butylene
Butoxy ethanol(2-)	00111-76-2	3.39E-01	NA	1.57E+03	butyl cellosolve
Butyl acetate(n-)	00123-86-4	8.46E-01	1.74E+00	4.61E+04	NA

TABLE 29. Irritancy Database II (Continued): Compound, Chemical Abstract Number[a], Odor Threshold (ppm)[b], Odor Threshold Standard Deviation (ppm), Vapor Pressure (ppm)[c],

Compound	Chemical Abstract Number	O_T (ppm)	O_T Std. Dev. (ppm)	Vapor Pressure (ppm)	Pseudonym
Butyl acetate(sec-)	00105-46-4	NA	NA	NA	acetic acid sec-butyl ester
Butyl acetate(tert-)	00540-88-5	NA	NA	NA	NA
Butylamine(n-)	00109-73-9	6.55E-01	5.54E-01	NA	NA
Butylbenzene(n-)	00104-51-8	NA	NA	1.35E+03	NA
Butylbenzene(tert-)	00098-06-6	NA	NA	2.53E+03	Dimethylethyl benzene (1,1-)
Butyltoluene(p-tert-)	00098-51-1	NA	NA	NA	NA
Chlorobenzene	00108-90-7	1.04E+00	7.96E-01	1.34E+04	NA
Chloroform	00067-66-3	2.67E+01	3.70E+01	2.64E+05	Trichloromethane
Chlororacetophe-none(alpha-)	00532-27-4	NA	NA	2.40E+02	Phenylacetyl chloride
Cyclohexane	00110-82-7	3.01E+01	2.50E+01	1.16E+05	NA
Cyclohexanol	00108-93-0	6.17E-02	NA	1.73E+03	NA
Cyclohexanone	00108-94-1	1.62E+00	2.70E+00	5.30E+03	NA
Decane(n-)	00124-18-5	7.41E-01	NA	2.01E+03	NA
Decyl acetate	NA	NA	NA	NA	NA
Dichlorobenzene(o-)	00095-50-1	1.47E-01	1.81E-01	1.61E+03	1,2-Dichlorobenzene
Dichlorobenzene(p-)	00106-46-7	4.79E-02	NA	2.27E+03	1,4-Dichlorobenzene
Dichloromethane	00075-09-2	5.62E+01	8.56E+01	5.96E+05	Methylene choride
Diethylamine	00109-89-7	3.14E-01	3.51E-01	2.99E+05	Diethylamine
Diisobutyl ketone	00108-83-8	3.39E-01	NA	NA	2,6-Dimethylheptan-4-one
Diisopropylamine	00108-18-9	4.04E-01	4.59E-02	NA	NA
Dimethylamine	00124-40-3	2.74E-01	4.76E-01	2.74E+06	NA
Dioxane(1,4-)	00123-91-1	6.10E+00	3.09E+00	4.75E+04	NA
Dipropylene glycol methyl ether	34590-94-8	NA	NA	NA	NA
Dodecane(n-)	00112-40-3	2.04E+00	NA	2.53E+02	NA
Dodecyl acetate	NA	NA	NA	NA	NA

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TABLE 29. Irritancy Database II (Continued): Compound, Chemical Abstract Number[a], Odor Threshold (ppm)[b], Odor Threshold Standard Deviation (ppm), Vapor Pressure (ppm)[c],

Compound	Chemical Abstract Number	O_T(ppm)	O_T Std. Dev. (ppm)	Vapor Pressure (ppm)	Pseudonym
Ethanol	00064-17-5	8.77E+01	1.51E+02	6.71E+04	Ethyl alcohol
Ethanolamine	00141-43-5	NA	NA	NA	NA
Ethoxyethanol(2-)	00110-80-5	1.26E+00	4.04E-01	NA	EGEE, ethyl glycol, cellosolve
Ethyl acetate	00141-78-6	4.68E+00	6.09E+00	1.13E+05	NA
Ethyl acrylate	00140-88-5	1.03E-03	7.05E-04	4.51E+04	Ethyl 2-propenoate
Ethylamine	00075-04-7	4.27E-01	3.89E-01	1.50E+06	NA
Ethyl amyl ketone	00541-85-5	NA	NA	NA	Ethyl n-amyl ketone
Ethylbenzene	00100-41-4	2.30E+00	NA	1.11E+04	
Ethylbutanal(2-)	00097-96-1	NA	NA	NA	
Ethylene	00074-85-1	3.69E+02	3.64E+02	1.53E+08	Ethene
Ethylenediamine	00107-15-3	NA	NA	1.43E+04	1,2-Ethanediamine
Ethylenimine	00151-56-4	NA	NA	NA	Aziridine
Ethyl ether	00060-29-7	NA	NA	7.95E+05	diethyl ether
Ethyl formate	00109-94-4	1.86E+01	NA	3.47E+05	NA
Ethyltoluene(2-)	00611-14-3	NA	NA	3.19E+03	NA
Ethyltoluene(3/4-)	NA	NA	NA	3.67E+03	NA
Formaldehyde	00050-00-0	3.12E+00	5.43E+00	5.66E+06	Methanal
Formic acid	00064-18-6	1.40E+02	2.03E+02	5.04E+04	NA
Furfural	00098-01-1	1.30E+00	1.55E+00	1.81E+03	2-Furaldehyde
Heptane(n-)	00142-82-5	1.06E+01	4.30E+00	5.51E+04	NA
Heptanol(1-)	00111-70-6	2.60E-02	8.26E-03	2.78E+02	n-Heptyl alcohol
Heptanol(4-)	NA	NA	NA	NA	NA
Heptanone(2-)	00110-43-0	1.56E-01	8.87E-02	1.70E+03	Methyl amyl ketone, methyl n-amyl ketone
Heptyl acetate	NA	NA	NA	NA	NA
Heptylamine(n-)	00111-68-2	NA	NA	NA	NA
Hexanal(n-)	00066-25-1	1.87E-02	1.51E-02	NA	caproic aldehyde, hexaldehyde

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TABLE 29. Irritancy Database II (Continued): Compound, Chemical Abstract Number[a], Odor Threshold (ppm)[b], Odor Threshold Standard Deviation (ppm), Vapor Pressure (ppm)[c],

Compound	Chemical Abstract Number	O_T (ppm)	O_T Std. Dev. (ppm)	Vapor Pressure (ppm)	Pseudonym
Hexane(n-)	00110-54-3	2.23E+01	3.97E+00	2.05E+05	NA
Hexanol(1-)	00111-27-3	1.12E-01	1.16E-01	1.20E+03	n-Hexyl alcohol
Hexyl acetate(n-)	00142-92-7	3.16E-01	NA	NA	NA
Hexyl acetate(sec-)	00108-84-9	NA	NA	NA	NA
Hexylamine(n-)	00111-26-2	NA	NA	NA	NA
Hexylbenzene(n-)	01077-16-3	NA	NA	NA	1-Phenylhexane
Isoamyl alcohol	00123-51-3	5.15E-02	2.82E-02	3.67E+03	3-Methyl-1-butanol
Isobutyl alcohol	00078-83-1	2.24E+01	6.47E+01	1.43E+04	2-Methyl-1-propanol
Isobutyraldhyde	00078-84-2	6.64E-02	7.69E-02	NA	Methyl propanal (2-)
Isopropyl acetate	00108-21-4	3.04E+00	2.71E+00	7.34E+04	NA
Isopropylamine	00075-31-0	6.76E-01	NA	NA	NA
Isopropyl ether	00108-20-3	NA	NA	2.18E+05	diisopropyl ether
Limonene	00138-86-3	4.37E-01	NA	2.34E+03	cyclohexene, 1-methyl-4-(1-methylethe-nyl)cyclohexene
Menthol	00089-78-1	9.09E-01	1.54E+00	1.27E+02	5-Methyl2-cyclohex-anol
Methanol	00067-56-1	2.61E+02	2.34E+02	1.53E+05	methyl alcohol, wood alcohol
Methyl-2-Propanol(2-)	NA	2.00E+01	2.24E+01	5.08E+04	Tert.butyl alcohol
Methyl-5-hexan-2-one	00110-12-3	4.17E-02	NA	NA	Methyl isoamyl ketone
Methyl acetate	00079-20-9	2.09E+01	2.55E+01	2.88E+05	NA
Methyl acrylate	00096-33-3	2.63E-02	NA	1.11E+05	Methyl 2-propenoate
Methylamine	00074-89-5	2.19E-02	-1.34E-02	4.11E+06	NA
Methylbutanal(3-)	00590-86-3	2.24E-03	NA	NA	Isovaleraldehyde
Methyl chloride	00074-87-3	1.02E+01	NA	8.11E+06	Chloromethane
Methylcyclohexane	00108-87-2	9.03E+02	NA	5.59E+04	NA
Methylcyclohexanol	25639-42-3	NA	NA	NA	NA
Methylcyclopentane	00096-37-7	NA	NA	1.79E+05	NA

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TABLE 29. Irritancy Database II (Continued): Compound, Chemical Abstract Number[a], Odor Threshold (ppm)[b], Odor Threshold Standard Deviation (ppm), Vapor Pressure (ppm)[c],

Compound	Chemical Abstract Number	O_T (ppm)	O_T Std. Dev. (ppm)	Vapor Pressure (ppm)	Pseudonym
Methyl ethyl ketone	00078-93-3	1.05E+01	8.74E+00	NA	2-Butanone
Methylhexane(3-)	00589-34-4	NA	NA	7.56E+04	NA
Methyl isobutyl ketone	00108-10-1	7.28E-01	5.85E-01	8.19E+03	4-Methylpentan-2-one
Methyl methacrylate	00080-62-6	5.83E-01	6.91E-01	4.67E+04	Methyl 2-methylprop-2-enoate
Methylstyrene(alpha-)	00098-83-9	1.54E-01	2.25E-02	5.12E+03	Isopropenylbenzene, cumene
Naphtalene	00091-20-3	3.01E-02	3.04E-02	4.29E+02	NA
Nitrobenzene	00098-95-3	1.45E-01	3.27E-01	3.07E+02	NA
Nonane(n-)	00111-84-2	2.36E+00	2.83E+00	5.44E+03	NA
Octanal	00124-13-0	1.81E-03	1.52E-03	6.59E+00	Carprylicaldehyde
Octane(n-)	00111-65-9	6.28E+00	3.04E+00	1.60E+04	NA
Octanol(1-)	00111-87-5	1.57E-02	1.86E-02	1.15E+02	Caprylic Alcohol
Octyl acetate	NA	NA	NA	NA	2-ethyl hectyl acetate
Pentanal(n-)	00110-62-3	9.22E-03	1.04E-02	NA	n-Valeraldehyde
Pentane(n-)	00109-66-0	3.40E+01	1.42E+01	7.99E+05	NA
Pentanol(1-)	00071-41-0	9.58E-01	1.43E+00	2.76E+03	amyl alcohol
Pentanol(iso-)	NA	NA	NA	NA	NA
Pentanone(2-)	00107-87-8	2.04E+00	1.53E+00	1.84E+04	methyl propyl ketone, methyl n-propyl ketone
Pentyl acetate	00628-63-7	7.61E-02	1.31E-01	NA	Amylacetate(n-)
Pentylamine(n-)	00110-58-7	NA	NA	NA	NA
Phenol	00108-95-2	3.77E-01	6.77E-01	5.00E+02	NA
Phenylethanone(1-)	00098-86-2	5.66E-01	6.14E-01	5.22E+02	Acetophenone, phenyl methyl ketone, acetyl-benzene, hypnone
Propanal(n-)	00123-38-6	4.51E-02	5.38E-02	NA	NA
Propanol(1-)	00071-23-8	3.90E+00	4.08E+00	2.28E+04	NA
Propanol(2-)	00067-63-0	1.30E+01	1.04E+01	5.07E+04	isopropyl alcohol
Propanone(2-)	00067-64-1	4.60E+01	6.87E+01	2.99E+05	Acetone

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TABLE 29. Irritancy Database II (Continued): Compound, Chemical Abstract Number[a], Odor Threshold (ppm)[b], Odor Threshold Standard Deviation (ppm), Vapor Pressure (ppm)[c],

Compound	Chemical Abstract Number	O_T (ppm)	O_T Std. Dev. (ppm)	Vapor Pressure (ppm)	Pseudonym
Propyl acetate	00109-60-4	1.07E+00	1.24E+00	3.84E+04	Acetic acid n-propyl ester
Propylamine(n-)	00107-10-8	1.10E-02	NA	4.37E+05	Propylamine
Propylbenzene	00103-65-1	NA	NA	3.97E+03	NA
Propylene	00115-07-1	5.52E+01	2.43E+01	2.05E+07	Propene
Propylene glycol monom-ethyl ether	00107-98-2	NA	NA	NA	1-Methoxy-2-propanol
Styrene	00100-42-5	1.73E-01	1.02E-01	8.51E+03	Vinylbenzene, Ethenyl benzene
Tetrachloroethane(1,1,2,2-)	00079-34-5	2.79E-01	1.45E-01	7.41E+03	NA
Tetrachloroethylene	00127-18-4	8.01E+00	7.16E+00	2.19E+04	perchloroethylene
Toluene	00108-88-3	2.24E+00	1.88E+00	3.35E+04	NA
Toluene 2,4-diisocyanate	00584-84-9	2.14E+00	NA	NA	NA
Trichlorobenzene(1,2,4-)	00120-82-1	NA	NA	4.98E+02	NA
Trichloroethane(1,1,1-)	00071-55-6	2.55E+01	1.48E+01	1.61E+05	Methyl chloroform
Trichloroethylene	00079-01-6	7.50E+00	7.74E+00	9.41E+04	Trichloroethene
Trichlorofluoromethane	00075-69-4	1.62E+01	NA	1.35E+06	Freon-11, fluorotrichlo-romethane
Trichloropropane(1,2,3-)	00096-18-4	NA	NA	3.36E+03	NA
Triethylamine	00121-44-8	3.22E-01	1.11E-01	NA	NA
Trimethylbenzene(1,2,3-)	00526-73-8	NA	NA	1.98E+03	NA
Trimethylbenzene(1,2,4-)	00095-63-6	1.86E-01	1.11E-01	2.49E+03	pseudocumene
Trimethylbenzene(1,3,5-)	00108-67-8	3.17E-01	2.69E-01	3.18E+03	mesitylene
Trimethylhexane(2,2,5-)	03522-94-9	3.53E+00[d]	NA	NA	NA
Undecane(n-)	01120-21-4	1.20E+00	2.53E-01	6.96E+02	NA
Xylene(m,p-)	NA	6.87E-01	NA	9.80E+03	NA
Xylene(o-)	00095-47-6	2.13E+00	3.26E+00	7.66E+03	Dimethyl benzene (1,2-)

a. NA (not applicable) indicates information not available.

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b. Values from data reported by Devos et al. (1990); ethylbenzene value deemed too low, used separate source (Amoore and Hautala, 1983).

c. Using temperature information from the CRC Handbook (Chemical Rubber Company, 1975), saturated vapor concentration was extrapolated from pressure (mm Hg) at human physiological temperature, (23° C).

d. * Trimethylhexane(2,2,5-) = O_T averaged from O_T for *n*-octane, *n*-nonane.

VOC Exposure Metrics and their Relationship to "Sick Building Syndrome" Symptoms

Introduction

The prevalence of "sick building syndrome" (SBS) has been found to be relatively high, even in buildings without known health problems. Cross-sectional studies, selected without regard for worker complaint, report overall prevalences to be greater than 20% (Hedge et al., 1989; Norback and Torgen, 1990; Skov et al., 1990; Mendell, 1991; Zweers et al., 1992). Human exposure chamber studies have strongly implicated TVOCs as a cause of SBS symptoms (Molhave et al., 1986; Kjaergaard et al., 1989).

In field studies with VOC concentrations at levels typically found in buildings, correlations generally have not been found between the usual VOC exposure metrics (e.g., TVOC, ΣVOC_i) and SBS symptoms. Norback et al. (1990) reported associations between total hydrocarbon (TVOC) and

airway (nasal), general and eye symptoms at TVOC levels of 130 $ug\ m^{-3}$; however, chemical measurements of indoor air quality had been performed after questionnaire data had been gathered (from 6 months to 4 years). Hodgson et al. (1991) reported VOC exposure (personal samplers) to be associated with IAQ complaints in a field study, but levels were not reported. Hodgson et al. (1992) reported associations between VOC concentrations and central nervous symptoms, but the relationship was weak when compared with associations between work stress and complaints. No associations with TVOC were found for three observational studies (Skov et al., 1990; Skov et al., 1990; Mendell, 1991). Sundell et al. (1993) reported negative correlations between TVOC and symptom prevalences. TVOC concentrations in the study by Sundell et al. were comparatively low (geometric mean values of 45 $ug\ m^{-3}$ over 29 buildings with a maximum of 740 $ug\ m^{-3}$) relative to CHBS VOC concentrations (geometric mean of 560 $ug\ m^{-3}$ over 12 buildings with a maximum of 7,000 $\mu g\ m^{-3}$). However, differences in TVOC concentrations are due to the different sampling and analysis methods for TVOC; Sundell et al. used solvent (dichloromethane[1]) extraction of samples collected on charcoal, while CHBS VOCs were thermally desorbed.

Prior efforts to characterize VOC exposure used the TVOC metric, which does not consider potencies of different mixtures. In the research reported here, a scale of relative irritant potencies for VOCs was developed, and used to create and test some alternative

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1. Dichloromethane is a much less efficient extraction solvent for charcoal compared to the usual carbon disulfide used to extract charcoal.

metrics of VOC exposure. The fundamental hypothesis of this research is that VOC metrics that take into account individual VOC potencies will be useful in a model of reported SBS symptoms even at low exposure levels. An additional hypothesis is that as unmeasured VOCs may cause observed symptoms, and as exposures to VOCs are to a mixture of compounds with shared sources, an irritant VOC that is not measured but emitted by the same source as a measured VOC will be correlated with other VOCs emitted by the source. Statistical techniques exist that can help identify sources of emissions and trace VOCs which have not been measured. Therefore, information on VOC potencies and sources can be used to develop additional metrics that may predict symptom outcomes at the levels experienced in nonindustrial office settings.

VOC Exposure Metrics

The current research investigates a number of exposure metrics for the complex mixtures of VOCs to which building occupants are exposed. Table 30 summarizes all VOC exposure metrics (name, description, equation) investigated. The most widely used metric is the mass sum of the VOCs (TVOC). A similar metric is the sum of the individually identified VOCs (ΣVOC_i). As described previously, the use of a capillary gas chromatograph connected via direct capillary interface to a mass spectrometer (GC-MS) allows for GS-MS analysis of individual VOCs, which are summed into the ΣVOC_i metric.

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TABLE 30. VOC Exposure Metrics: Name, description, equation

Metric Name	Description	Equation
TVOC	Total VOCs, sum by mass of VOCs.	No equation, mass sum as per GC-MS (TIC)[a] or FID.
ΣVOC_i	Sum of individual VOCs quantified by GC/MS.	$$\sum_i^n voc_i$$
Irritancy/ΣVOC_i	Sum of irritancy-weighted individual compounds. Irritancy weighting based on irritancy relative to toluene. See Table 27 in "Sensory Irritants: VOCs".	$\sum_i^n r_i \cdot VOC_i$ where: r_i = Irritancy weighting for VOC_i
Odor/ΣVOC_i	Sum of odor-weighted individual compounds. Odor weighting was based on odor relative to toluene[b].	$\sum_i^n o_i \cdot VOC_i$ where: o_i = Odor weighting for VOC_i
Chemical Class	Concentrations of individual compounds summed into five chemical classes: Aromatic Hydrocarbons, Alkanes, Terpenes, Chlorinated Hydrocarbons, Oxidized Hydrocarbons. Five coefficients for classes were fit by multivariate logistic regression analysis against symptoms (controlling for confounders).	$\beta_1 (AromaticHC) + \beta_2 (Alkane) + \beta_3 (Terpene) + \beta_4 (ChlorinatedHC) + \beta_5 (OxidizedHC)$ where: $AromaticHC$ = Sum of concentrations of Aromatic Hydrocarbons; $Alkane$ = Sum of concentrations of Alkanes; $Terpene$ = Sum of concentrations of Terpenes; $ChlorinatedHC$ = Sum of concentrations of Chlorinated Hydrocarbons; $OxidizedHC$ = Sum of concentrations of Oxidized Hydrocarbons; β_i = regression coefficients of the chemical classes.
Irritancy/PC	VOCs preselected based on irritant order as per relative irritancy scale, and the resultant 4 principal components from principal component analysis.	$\beta_1 P^{(1)} + \beta_2 P^{(2)} + \beta_3 P^{(3)} + \beta_4 P^{(4)}$
Source/PC	VOCs preselected based on known sources, and the resultant 4 principal components from principal component analysis.	$\beta_1 P^{(1)} + \beta_2 P^{(2)} + \beta_3 P^{(3)} + \beta_4 P^{(4)}$

a. Total ion current (TIC), i.e., everything under the chromatogram curve.

b. Odor thresholds were ordered relative to toluene using the same method as described for irritancy; however, the results were not shown. A VOC metric based on odor would use the compounds that dominate the odor of the mixture. CHBS VOCs were well below odor threshold; i.e, no odor(s) dominated. As an odor threshold ordered scale may not be valid due to low exposure levels, the relative ordered scale based on odor was not reported, although it was used in an exploratory manner to test the usefulness of an odor-weighted metric.

In the current research, potency is addressed by several different metrics. The Irritancy/ ΣVOC_i and Odor/ΣVOC_i exposure metrics are defined as the sum of individual compounds weighted by their relative potencies, based on irritancy or odor thresholds, respectively. The Chemical Class metric is composed of individual VOCs summed into five different chemical classes commonly found indoors: aromatic hydrocarbons; alkanes; terpenes (limonene); chlorinated hydrocarbons, oxidized hydrocarbons. Coefficients for each class were fitted by regression analysis against reported symptoms.

The primary metrics in terms of the main hypotheses were Irritancy/PC and Source/PC metrics, which were developed using principal component analysis. Principal component analysis (Appendix D) was used to replace the underlying highly correlated structure of multiple VOCs in a complex mixture, measured at each of 22 sites, to a smaller number of uncorrelated VOC vectors which could be linked with VOC sources. Computer algorithms utilized in this technique iteratively develop principal components (vectors), which are by definition uncorrelated. The statistical technique has two important properties: 1) the principal components are sums that condense information from the original multivariate measurements; 2) the principal components are uncorrelated measures that can be used as variables for input into further analyses.

Development of Irritancy/PC and Source/PC Metrics

In principle, all available measured VOCs could be used in the principal component analysis. For the CHBS data set, however, there were only 22 cases (sites) for which a complete set of VOC measurements and symptoms were available. To obtain a robust

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principal component solution, a smaller subset of VOCs was selected. For the Source/PC metric, VOCs were chosen for inclusion using the criterion of potential source strength, as indicated by the magnitude of the Indoor/Outdoor (I/O) ratio ("The California Healthy Building Study"). That is, the 10 VOCs with the highest or lowest I/O ratios were selected. VOCs with high I/O ratios have predominant indoor sources; conversely, VOCs with low I/O ratios have strong ambient sources. This method selected for compounds with the strongest sources (indoor or outdoor). Four sources identified previously based on I/O ratios included motor vehicle emissions, room freshener/deodorizer, building materials, and cleaning products. These four vectors together comprised the Source/PC metric.

For the Irritancy/PC metric, the most irritating CHBS VOCs were chosen based on the relative irritant scale (Table 27). However, for the Irritancy/PC metric, prior source identification was also used to select VOCs. Specifically, 5 of the 10 most irritating compounds identified in Table 27 were from a suite of compounds previously identified to be due to motor vehicle emissions (Daisey et al., 1994). An important hypothesis of this research is that the principal component analysis method allows for identification of sources important in a model of irritant SBS symptoms. Therefore, in order to allow inclusion of VOCs from more than one identified source, three irritating VOCs (1,2,4-trimethylbenzene, *m/p*-xylene, *o*-xylene) associated with the motor vehicle emissions source were chosen to be representative of this source. This choice allowed inclusion of other compounds, which would be representative of emissions from other sources, for use

in the principal component analysis. The additional VOCs selected were styrene,

ethylacetate, butylacetate, n-hexanal, n-pentanal, 2-butoxyethanol, 2-propanol.

After selection based upon relative irritancy and prior source identification, 10 VOCs

were entered into principal component analysis of 22 observations. Between the fourth

and fifth principal components the eigenvalues dropped from 1.1 to 0.73, and rapidly

decreased to less than 0.001; four components were retained for interpretation. These four

accounted for 84% of the total variance in the data set; therefore, a reduction in the data

from 22 observations on 10 variables to 22 observations on 4 principal components is

reasonable[1]. Table 31 presents results from the principal component analysis.

TABLE 31. Irritancy/PC Metric: Principal Component Analysis

Compounds	Principal Components				Communality
	1	2	3	4	
Styrene	0.03	0.042	0.81	-0.015	0.83
Ethyl acetate	-0.32	0.46	0.12	-0.25	0.91
Butyl acetate	0.29	0.098	0.079	0.29	0.45
1,2,4-Trimethylbenzene	0.42	0.29	0.065	-0.23	0.89
m/p-Xylene	0.42	0.27	-0.10	-0.29	0.96
o-Xylene	0.42	0.29	-0.11	-0.24	0.98
n-Hexanal	-0.34	0.46	0.13	-0.062	0.89
n-Pentanal	-0.40	0.33	-0.27	-0.14	0.97
2-Butoxyethanol	0.069	0.33	-0.36	0.564	0.74
2-Propanol	0.069	0.34	0.27	0.563	0.68
Variance (%)	42	17	12	11	Overall 84%
Probable Source Type	Motor Vehicle Emissions	Building Materials	Carpet/ Building Materials	Water-based Paints and Solvents	

Several of the VOCs entered into the principal component analyses were shared in

common between the Source/PC and Irritancy/PC metrics; consequently, some of the

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1. Following identification of the individual principal components, these results are confirmed using the original full VOC data set.

sources identified were the same. The first principal component of the Irritancy/PC metric, identified as motor vehicle emissions, accounted for 43% of the variance in the data, and the second principal component, building materials, accounted for 17% of the variance (both identified in "Descriptive Statistics: VOCs"). The third and fourth principal components, identified below, accounted for 12% and 11% of the variance, respectively.

Carpet/Building Materials Source

The variable most strongly and positively correlated with the third principal component was styrene (0.81). I/O ratios indicated there were strong indoor sources of styrene in Buildings 4, 5.2, 5.6, and 10. This principal component has been identified as originating from latex backing used for carpets, and building materials, a "carpet/building materials" source.

For styrene, I/O ratios were greater than 5 for Buildings 4, 5.2, 5.6, and 10; I/O ratios were most elevated (I/O = 13) for Buildings 4 and 10. Carpet is a known indoor source of styrene (Miksch et al., 1982; Wallace et al., 1987; Seifert et al., 1989; Hodgson et al., 1992; Hodgson et al., 1993). Other sources of styrene include various building materials: unspecified building materials (Berglund et al., 1989), polystyrene foam insulation (Sheldon et al., 1988), plywood (Monteith et al., 1984), particle board (Monteith et al., 1984), rubber floor covering (Wolkoff et al., 1990), solvents (Wallace, 1986), adhesives (Girman et al., 1986; Seifert et al., 1989). Styrene is also found in environmental tobacco smoke (Hodgson et al., unpublished data), and in the exhaled breath of smokers (Wallace et al., 1985; Wallace, 1986; Wallace et al., 1986; Wallace et al., 1988). As the buildings

were all from nonsmoking county buildings, environmental tobacco smoke (sidestream or exhaled breath) could not be the source of the styrene. Therefore, for the CHBS buildings, possible sources of styrene were carpet and building materials (insulation, rubber floor covering, plywood, particle board, solvents, and adhesives).

In the CHBS buildings, indoor styrene levels track well with carpet age. Specific information on carpet age was collected by inspection of the study spaces and through interview of appropriate building personnel (Fisk et al., 1994). Of the buildings, Buildings 4 and 10 had the highest I/O ratios for styrene (I/O = 13). The newest carpets were located in two sampling spaces in Building 4; carpets in space numbers 41 and 42 were 1.5 and 2 years, respectively[1] (Mendell, 1995). A 2-year old carpet was installed on one floor of Building 10 (Fisk et al., 1994). Carpet ages in other buildings ranged from 4 to 15 years. I/O ratios for styrene were 5 for Building 5.2 and 5.6 but carpet age was 12 years; therefore, building materials were the more likely source of indoor styrene levels in Building 5.2 and 5.6.

In summary, principal component 3 was identified as a carpet/building materials source based on the strong coefficient for styrene, and based on the sources reported for styrene in office buildings. I/O ratios for the compound associated with principal component 3 indicated indoor sources dominated in the same subset of buildings (4, 5.2, 5.6, and 10). Styrene is a known marker for emissions from the backing used for carpets. Styrene

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1. Environmental samples were not taken in the two spaces with 1 year old carpet (43 and 44), but other samples collected on this floor may have reflected contributions from these newer carpets due to proximity. Additionally, as Building 4 was air conditioned, styrene was likely recirculated and redistributed from its source space to other spaces in the building via the ventilation system.

tracked well with age of carpets in the buildings; carpet ages were youngest (2 years or less) where styrene I/O ratios were most elevated (I/O = 13 for Buildings 4 and 10). Therefore, principal component analysis, I/O ratios, information on potential indoor sources, and carpet age were consistent with identification of this principal component as a carpet/building materials source.

Water-based Paints and Solvents Source

The variables most highly and positively correlated with the fourth principal component were 2-butoxyethanol (0.564) and 2-propanol (0.563). This principal component was identified as a water-based paint and solvent source, based on the combination of the coefficient for 2-butoxyethanol and the presence of this compounds together with 2-propanol in formulations of water-based paints and latex (soap) formulations. 2-Butoxyethanol[1] is an important constituent in paint additives (binders) used in US water-based paints (Noyes Data Corporation, 1981), and is a component of emissions from paints representative of the US market (Sheldon and Pellizzari, 1994). 2-Butoxyethanol and 2-propanol have also been reported as raw materials in coalescing solvents (i.e., binders) used in Danish water-based paints (Hansen et al., 1987). Glycol ethers (2-butoxyethanol) and their acetate derivatives are widely used as solvents in the manufacture of paints, lacquers, and varnishes, as well as adhesives and liquid soaps (Hodgson and Wooley, 1991). The CTCP database reported over 80 consumer products

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1. 2-Butoxyethanol is also known as ethylene glycol monobutyl ether, ethylene glycol butyl ether, butyl cellosolve; the compound is uniquely identified by its chemical abstract number: 111-76-2.

that contained 2-butoxyethanol, over half of which were cleaning compounds (Clinical Toxicology of Commercial Products, 1990).

The I/O ratios suggest indoor sources of 2-butoxyethanol were dominant in Buildings 3 and 7 through 12. I/O ratios for 2-butoxyethanol are less than 1.0 for Buildings 4, 5.2 and 5.6, while I/O ratios were 3 - 21 for Buildings 3, 7 through 12. The set of buildings with high I/O ratios for 2-butoxyethanol was different than the set of buildings with high I/O ratios for the compound identified as associated with carpet and building materials source.

Noyes Data Corporation (1981) has published detailed descriptive information on patents, issued since February 1978, that deal with paint additives used by the US paint industry. A primer patented by E.I. Du Pont de Nemours and Company (Du Pont) is prepared using 2-butoxyethanol (ethylene glycol monobutyl ether) as an important constituent. The primer is composed of: a binder of alkyd resin, 2-butoxyethanol (319 parts by weight out of 10,000), cobalt naphthenate solution, drier stabilizer solution, methyl ethyl ketoxime, deionized water, triethyl amine, and water-based dispersed pigments (7,053 parts by weight out of 10,000). The water-based pigment dispersion formulation itself contains 2-butoxyethanol (35 parts by weight out of 10,000) as 1 of 10 ingredients. The resulting primer is sprayed onto substrates (i.e., metal, polyester, plastics) and dried at room temperature for about 60 minutes. Conventional finishes of acrylic paints can be applied to metal substrates having a coating of the above primer.

In addition to additives in US paint formulations, 2-butoxyethanol was reported as a major component in emissions of US paints (Sheldon and Pellizzari, 1994). The US Environmental Protection Agency reported VOC emissions from various types of products used indoors, specifically VOC emissions from indoor architectural coatings (paint). As the main goal of the study was to evaluate testing methods, the report is not a summary of all coatings used in the US; however, the paints were chosen to be broadly representative of the US market[1]. The report identified major chromatographic peaks in 6 latex paint samples (gloss, semigloss and flat); 2-butoxyethanol and ethylene glycol were found as major compounds in all paints sampled. Of the identified compounds, half were glycol ethers (7/14). Only major peaks were identified; 2-propanol was not listed as a major component of the tested paints.

Hansen et al. (1987) comprehensively reviewed the chemistry and toxicology of water-based or latex paints chosen from the Danish market in collaboration with the Danish Painters Union and the Danish National Institute of Occupational Health. Product types in the review represented 90% of the water-based paint used in Denmark. The researchers reported the percent by weight of formulations of paints and the determinations made during use of concentrations of various constituents of water-based paints. 2-Butoxyethanol (ethylene glycol butyl ether) and 2-propanol were found to be present as raw materials in coalescing agents in water-based paints at 1.4 and 0.01 percent by weight, respectively.

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1. Paints were chosen from manufacturers with a combined 29% of market share for architectural coatings (Sheldon and Pellizzari, 1994).

The researchers also reported VOCs measured in the air of 15 workplaces during application of water-based paints. The researchers reported both VOC concentrations in the air of the workplaces, and the content (weight percent) of these VOCs in the applied paint. According to the list of ingredients, VOCs found in paint included 2-butoxyethanol and styrene, but styrene was not found in the air during work with water-based paints. 2-Propanol was present as a raw material in the coalescing solvents/cosolvents used in water-based paints. 2-Butoxyethanol was 0.0-1.4 percent by weight of the applied paint. In the air of the work area, the concentration of 2-butoxyethanol was 2-60 mg m^{-3}. Several other glycol ethers were also measured in the workplace air, but not 2-propanol.

The presence of 2-butoxyethanol in paint formulations was confirmed by two other studies. Two of five water-based paints tested emitted 2-butoxyethanol in controlled environmental chamber experiments over a one-year period (Clausen et al., 1990). Six low-emitting paints and varnishes from West Germany contained up to 6% by weight of 2-butoxyethanol (Plehn, 1990).

2-Butoxyethanol has been linked to building materials in complaint buildings. Glycol ethers were found in samples of linoleum from a complaint building; 2-butoxyethanol was present along with diethylene glycol ethyl ether and diethylene glycol butyl ether (Wolkoff et al., 1993). 2-Butoxyethanol was measured over several sampling periods from summer 1987 to spring 1988 in a building with health complaints, and ranged from 1.8 - 34 ug m^{-3} (Weschler et al., 1990).

Riala and Riihimaki (1991) measured exposures to solvents during normal installation and varnishing work of Finnish parquet and carpet fitters. During 16 working days between April and September 1987, measurements were taken at 13 construction sites of 3 parquet and 3 carpet firms. Activated charcoal tubes with low-flow sampling pumps were used to sample ambient air; VOCs were analyzed using GC and FID. Propylene glycol monomethyl ether (a glycol ether) was measured in the ambient air during parquet work; however, exposures to propylene glycol monomethyl ether were low - only 15 ppm during undercoat varnishing.

Identification of the fourth principal component as a water-based paints and solvents source was based on several observations. 2-Butoxyethanol, strongly correlated (0.564) with principal component 3, has been found as an important component of water-based paints as well as several consumer cleaning products. 2-Butoxyethanol is used as a paint additive in a primer formulation patented by Du Pont, a US chemical company. In a US study of paint formulations used by manufacturers with a combined 29% of the US market share, 2-butoxyethanol was a major component of several tested paints. In a comprehensive Danish review, 2-butoxyethanol and several other glycol ethers/acetates were found to be components of water-based paints. 2-Propanol, also highly associated with the fourth principal component (0.563), was one of the raw ingredients of coalescing solvents used in the paints.

It is likely that the 2-butoxyethanol is a tracer for other compounds not actually sampled in the CHBS study, specifically semivolatile VOCs (SVOCs); i.e., compounds whose boiling

points (b.p.) range from 240° C to 400 ° C. Hansen et al. (1987) reported compounds

found in both water-based coalescing solvents and water-based paints in workplace air

sampled during painting were: diethylene glycol butyl ether (b.p. 230 ° C), diethylene

glycol methyl ether (b.p. 193 ° C), dipropylene glycol methyl ether (b.p. 229-232 ° C), 2-

butoxyethanol (b.p. 171 ° C), ethylene glycol phenyl ether (b.p. 245 ° C), and propylene

glycol (b.p. 188 ° C). These compounds span the upper end of the VOC, and lower end of

the SVOC, range of volatilities. Due to their high molecular weight and boiling points,

SVOCs would not be detected using conventional VOC sampling and analysis methods.

Therefore, the 2-butoxyethanol found in this study is probably acting as a tracer for other

compounds emitted by water-based paints and solvents, and it is likely that the principal

component developed here can be used as a surrogate for these unmeasured compounds to

relate to symptom outcomes.

Confirmation of Source Identifications for Reduced Data Set

Johnson and Wichern (1988) previously showed principal component analysis could be

used to summarize sample variation reasonably well using three-fold number of variables

to cases[1]. In the California study, the original VOC data set contained 32 samples across

12 buildings. As described previously ("VOC and Subject Database"), due to temporal or

spatial discontinuity with subjects, not all VOC data could be used in the final joint VOC

and symptom database. However, as the original VOC data set (N=32) allows a three-fold

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1. Johnson and Wichern (1988) reported reliable results from principal component analysis on 5 variables with 14 observations (page 375).

number of cases to VOCs for the principal component analysis, the original data set can be

used to confirm identification of sources common to the 12 California buildings.

Presented in Table 32 are results of the principal component analysis on the same sub-set

TABLE 32. Irritancy/PC Metric: Principal Component Analysis on all VOCs (N=32)

Compound	Principal Component				Communality
	1	2	3	4	
Styrene	0.11	-0.16	0.10	0.74	0.86
Ethyl acetate	-0.30	0.23	0.54	0.07	0.91
Butyl acetate	-0.002	-0.51	0.42	-0.19	0.46
1,2,4-Trimethylbenzene	0.46	0.18	0.26	0.033	0.98
m/p-Xylene	0.44	0.21	0.25	-0.22	0.97
o-Xylene	0.45	0.24	0.23	-0.18	0.98
n-Hexanal	-0.35	0.32	0.33	0.10	0.86
n-Pentanal	-0.41	0.29	0.16	-0.23	0.92
2-Butoxyethanol	0.034	0.55	-0.42	0.043	0.83
2-Propanol	0.084	0.20	0.14	0.52	0.86
Variance (%)	37	23	15	12	Overall 88%
Probable Source Type	Motor Vehicle Emission	Water-based Paints and Solvents	Building Materials	Carpet/ Building Materials	

of VOCs using the original full set of VOC measurements for 32 sites. The principal

component analyses from both the full (N=32) and limited (n=22) VOC data sets

identified the same compounds as being highly associated with four sources: motor

vehicle emission, water-based paints and solvents, building materials, and carpet/building

materials. Coefficients presented in Table 32 reflect the pattern of coefficients from Table

31. The water-based paints and solvents source was found to incorporate more of the

variance (23%), while the variance represented by the carpet/building materials source did

not change (12%). The same sources were identified using either two-fold (n=22), or

three-fold (N=32), number of cases to number of variables (n=10). The findings from the

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current analyses support the general approach that use of a minimum of two-fold number of cases to variables will assure reliable principal component results.

Analytic Methods

As part of Phase 1 of the California Healthy Building Study (CHBS) (Daisey et al., 1990; Mendell, 1991; Fisk et al., 1993), concentrations of TVOC and of 39 individual VOCs were measured in 12 office buildings in the San Francisco Bay Area in Northern California. The data for the current investigation of the relationships between occupant symptoms and various metrics of exposure to VOCs are a subset of the original survey of 880 individuals. Not all individuals were located within reasonable proximity to VOC sampling locations; the final joint VOC and symptom database contained 517 individuals located in 12 buildings with 22 VOC samples.

Analyses were performed using Stata version 3.1. A symptom (Table 18) was considered work-related if it was reported as being experienced within the office building, but improving on days not in the office. Binary symptom outcomes (yes/no) were based on whether individuals experienced a work-related symptom three or more days "last week", where questionnaire administration was timed so that "last week" would be the week of VOC sampling.

Individual work-related symptoms are from individual symptom questions on the questionnaire: dry, irritated or itching eyes (eye); dry or itchy skin (skin); dry or irritated

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throat (throat); chest tightness (chest); difficulty breathing; runny nose; stuffy nose; sleepiness; fatigue; headache. Subjects were also queried regarding three symptoms believed not to be part of the SBS syndrome (earache, shoulder pain or numbness, toothache), to obtain some indication of symptom over-reporting.

Composite symptom variables were developed based on at least one positive report of any of the specified individual work-related symptoms. The irritant symptom variable was composed of eye, skin, or throat symptoms. The irritated mucus membrane variable was composed of eye, throat, runny nose, or stuffy nose symptoms. The overall variable was composed of general systemic symptoms (tight chest, difficulty breathing, runny nose, stuffy nose, sleepiness, fatigue, or headache).

Multivariate logistic regressions (Appendix E) were used to assess the relationships between work-related symptoms and various measures of VOC exposures, as determined by VOC metrics. Symptom prediction can be discussed in terms of the odds of observing a symptom given the presence of risk factor(s), versus the odds of observing a symptom without the presence of risk factor(s), or more simply as the Odds Ratio (OR). ORs were used as the measure of effect for both crude analyses (not adjusted for other potential risk factors or confounders) and adjusted analyses (adjusted for other potential risk factors or confounders). Crude ORs were estimated for each of 10 individual work-related symptoms, 3 non-SBS symptoms, and 3 composite symptoms. Adjusted ORs, estimated using multivariate logistic regression analysis, were calculated for all symptoms as a function of potential risk factors (or confounders). Additionally, the importance of the

independent variables on the effect of the odds ratio was evaluated in terms of the values

of the regression coefficients, per unit increase (Appendix F).

Variables Included in the Model

Variables were included in the full models (adjusted analyses) based on their potential

impact on VOC concentrations; i.e., the potential to confound or obscure relationships

between VOC exposures and SBS symptoms. Listed by groups below are the variables

considered as potential risk factors or confounders. Categorical independent variables

were represented by dichotomous indicator variables for each level; the reference levels

were not included in the model. An advantageous aspect of the logistic regression model is

that there is no need to categorize continuous variables.

Selected subsets of variables considered for the adjusted model included:

- VOC metrics;
- demographic (gender, age, race, education, job);
- potential indicators of source of exposures to VOCs (time using ncr paper, time using a copy machine, new paint nearby);
- potential biological cause of symptoms (median level of bacteria, median level of fungi);
- building (ventilation type, building age);
- temporal (perception of hot, perception of cold, temperature, relative humidity);
- sensitive subpopulations (asthmatics, individuals with allergies, ever smokers, problem building status).

All demographic variables were included. Female gender has been found to be associated

with higher symptoms (Hedge et al., 1989; Skov et al., 1989; Burge et al., 1990; Skov et

al., 1990; Jaakkola et al., 1991; Mendell, 1991; Zweers et al., 1992; Stenberg et al., 1993),

and gender differences to sensory irritants have been observed. For example, females on

average display the reflex response of momentary apnea at lower threshold concentrations

when exposed to sensory irritants (Garcia-Medina and Cain, 1982). Similarly, in a study of reduced sensitivity to CO_2 irritation in cigarette smokers, while both male and female smokers gave elevated thresholds relative to sex-matched controls, females had lower thresholds for the reflexive interruption of inhalation (Dunn et al., 1982). Gender was referenced to male.

Job status addressed potential effects of job type on symptom reporting; five job categories were referenced to managerial job category - professional, technical, clerical, case worker, and other category. Reported symptoms have been shown to be related to job categories and/or personal activities (Skov et al., 1989; Wallace et al., 1989; Hodgson et al., 1991; Clobes et al., 1992), although a comprehensive review of a specific job factor (clerical job) in studies of buildings found "sparse or inconsistent findings" (Mendell, 1993).

Although none has been identified as a causative factor of SBS, demographic variables such as age and race can affect symptom reporting, and were also included to allow for comparison across different studies. However, due to the large number of variables in the model, three demographic variables were simplified to dichotomous variables. Age was referenced to individuals less than 40 years old. Race was referenced to Caucasian. Education was referenced to high school graduate or less years of high school.

Potential effects of building characteristics or activities in offices on symptom reporting, the presence of new paint within 15 feet last year and minutes spent at the photocopier,

were included in the model. The activity of painting (Wieslander et al., 1994), or the odor of paint (Wallace et al., 1993), have been found to be associated with higher symptom prevalence. At the time of the survey, direct inspection by researchers identified on-going painting in several of the buildings (Fisk, 1995). Therefore, the remembered exposure to nearby paint was considered an important potential bias. Photocopier use (Skov et al., 1989; Mendell, 1991), presence of photocopier in the room (Sundell et al., 1994), and photocopier odor (Wallace et al., 1993) have been found associated with increased symptoms. Liquid-process photocopiers have been found to be sources of VOCs in office buildings (Miksch et al., 1982; Tsuchiya and Stewart, 1990; Hodgson et al., 1991), and two sites in the California buildings had liquid-process photocopiers. Therefore, time spent at the photocopier (any photocopier) was also included in the model.

Information on use of carbonless copy paper was not used, as few individuals appeared to understand the question (Mendell, 1995). Over 300 responses to the question on use of carbonless copy paper were either missing or zero minutes, 182 and 163 responses, respectively. By comparison, only 56 responses to the previous question on time spent photocopying were either missing or zero minutes, 36 and 20, respectively.

Potential effects of microbial organisms on symptom reporting were not included in the model. Measurements of these bioaerosols are very short term (15 or 30 minutes) and therefore not representative of an 8-hour work day. Additionally, measurements of bioaerosols in the CHBS were made up to one month after other environmental measurements.

For this study, levels[1] of total viable bacteria and fungi were low, 70-264 cfu m^{-3} and 5-85 cfu m^{-3}, respectively. Tolerable levels of general mold spores in indoor air were reported for exposures of 1000 cfu m^{-3} (Brief and Bernath, 1988). Even when levels of bioaerosols have been found to be extremely high, associations between symptoms and airborne endotoxin levels determined from microbial samples have been inconsistent. Positive associations were found between lung function changes and high levels of gram-negative bacteria and endotoxins experienced in the occupational exposure setting of pig farms (Heederik et al., 1991). Aggressive sampling showed a dose-response relationship between microbials and throat irritation, dry cough and itchy skin (Rylander et al., 1992). Gram-negative rods were found in higher numbers in the "sick" buildings (Teeuw et al., 1994). However, other studies have reported no association with total viable bacteria or fungi (Skov et al., 1990; Skov et al., 1990; Mendell, 1991). Given the inconsistency of previously reported associations, and uncertainties due to sampling of the current study, fungi and bacteria were not included in the model.

Of the two building characteristics (building age and ventilation type), only ventilation type has been found to be strongly correlated with symptoms in previous studies. Consistently higher symptoms have been reported in buildings with air-conditioning ventilation (Hedge et al., 1989; Skov et al., 1990; Mendell, 1991; Zweers et al., 1992). Ventilation category was represented in the current study by indicators for air conditioning ventilation and mechanical ventilation, referenced to natural ventilation.

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1. Bioaerosols levels were reported in median counts of colony forming units per cubic meter (cfu m^{-3}).

Of the temporal variables considered for inclusion (perception of hot, perception of cold, temperature, relative humidity), only continuous variables temperature and relative humidity were included. Studies on the effect of low humidity have found little effect or inconsistent findings (as per Mendell (1993)). Elevated temperature has been found to be positively associated with symptoms in previous studies (Skov et al., 1990; Skov et al., 1990; Jaakkola et al., 1991; Menzies et al., 1993). Other studies have found no association between temperature and symptoms (Norback and Torgen, 1990; Hodgson et al., 1991; Mendell, 1991; Hodgson et al., 1992; Zweers et al., 1992; Hall et al., 1993). Perception of temperature has been observed to be associated with symptoms and has been suspected to be related to symptoms (Fisk, 1995; Mendell, 1995). Therefore, actual temperature and humidity measurements were included instead of variables on perceived thermal comfort.

Sensitivity to irritant chemicals can be modified by preexisting physical or psychological sensitization (asthma, allergies, smoking history, or complaint building status). Asthma is a hyperactive response of the respiratory system to airborne irritants, causing airway constriction due to mucus secretion and airway constriction. The exact cause of asthma is still undetermined, although there are indications that it is a reaction to various allergens. A human chamber experiment on exposure of asthmatics to VOC mixtures (0, 2.5 and 25 $ug\ m^{-3}$) showed decreased forced expiratory velocity (FEV) as a percent of baseline, although the decline in FEV was not statistically significant from decline from sham exposure (Harving et al., 1991). Due to the small number of doctor-diagnosed asthmatics in the study, individuals with self-diagnosed hay fever[1] were also included in the

definition of sensitive subpopulation status. Although sensory science researchers have reported decreased sensitivity to irritants due to smoking (Dunn et al., 1982; Cometto-Muniz and Cain, 1992), status as a smoker has been also been found to be associated with higher symptoms (Skov et al., 1989; Norback and Torgen, 1990; Mendell, 1991). Accordingly, the presence or absence of sensitive subjects was indicated by a dichotomous variable. Individuals with either doctor-diagnosed asthma or self-diagnosed hay fever were referenced to absence of both sensitivities. Current or prior experience as a smoker (ever smoked) was referenced to never smoked. Finally, as knowledge of building complaint status can bias symptom reporting upwards, problem building status (referenced to location in other than the problem building) was included in the model.

Results

The effectiveness of the VOC exposure metrics in a model of SBS symptoms was evaluated by chi-square comparisons of likelihood statistics of models with and without the VOC metric (Appendix G). The results for each exposure metric, TVOC, ΣVOC_i, Irritancy/ΣVOC_i, Odor/ΣVOC_i, and Chemical Class, are presented in Table 33. None of these exposure metrics were significantly associated with SBS symptoms ($p > 0.05$), although ΣVOC_i was associated slightly with eye and skin symptoms ($p < 0.10$).

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1. Prevalence of allergic rhinitis (hay fever) and other allergic diseases in the United States is about 20 percent (Committee on the Health Effects of Indoor Allergens and Division of Health Promotion and Disease Prevention, 1993).

TABLE 33. TVOC and other VOC exposure metrics in a model: Chi-square comparisons of maximum log-likelihood estimations, with and without metrics[a]

Symptom	TVOC			ΣVOCi			Irritancy/ ΣVOCi			Odor/ΣVOCi			Chemical Class		
	X^2	p <	N	X^2	p <	N	X^2	p <	N	X^2	p <	N	X^2	p <	N
Eye	2.5	0.12	399	3	0.08	397	0.4	0.51	403	0.2	0.63	403	4	0.55	403
Skin	1.2	0.26	393	3	0.08	388	0.1	0.77	395	0.1	0.78	395	2.5	0.78	395
Throat	0.9	0.34	392	0.4	0.55	389	0.3	0.56	395	0.1	0.81	395	4.7	0.45	395
Irritant	2	0.15	412	1.6	0.2	409	0	0.99	416	0	0.86	416	3.4	0.64	416
Chest Tightness	!			3.5	0.06	344	1.1	0.29	350	0.1	0.75	350	6.3	0.28	350
Difficulty Breathing	!			0.1	0.73	367	0.2	0.63	373	0	0.94	373	7	0.22	373
Runny Nose	1.9	0.17	400	0	0.91	398	0.5	0.5	404	0	0.99	404	7.7	0.17	404
Stuffy Nose	2.8	0.09	392	0.4	0.52	389	0.2	0.66	395	0.1	0.83	395	8.1	0.15	395
Sleepiness	2.6	0.11	395	1.6	0.2	380	0.1	0.76	386	0	0.91	386	4.1	0.54	386
Fatigue	0.5	0.47	400	2.1	0.15	397	2.2	0.14	403	0.3	0.56	403	2.5	0.78	403
Headache	0.6	0.42	396	0.3	0.55	393	0.1	0.73	399	0.1	0.71	399	1	0.96	399
Overall	3.1	0.08	421	0.6	0.43	419	0	0.92	425	0.2	0.67	425	4.4	0.5	425
Irritated Mucous Membrane	21.1	0.15	415	1.9	0.17	413	0	0.88	419	0	0.84	419	10.1	0.07	419
Ear	!			!			!			!			!		
Shoulder	!			0	0.89	386	1.1	0.29	392	0.1	0.71	392	4.1	0.53	392
Tooth	!			!			!			!			!		

a. "!" indicates maximum likelihood statistics could not be estimated.

The Irritancy/PC and Source/PC exposure metrics were effective in prediction of SBS symptoms in a logistic model. However, although both the Irritancy/PC and Source/PC metrics contained 4 principal components, a simpler model based on a reduced number of principal components was found to be useful for both metrics. Individual source vectors were identified as more useful than others in symptom prediction based on their regression coefficients from the logistic model. For the Irritancy/PC metric, only the carpet/building materials and the water-based paints and solvents sources showed statistically significant regression coefficients in the logistic regression model. Similarly, for the Source/PC metric, only the cleaning source showed statistically significant regression coefficients in

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a logistic regression model. Simplification of the Irritancy/PC and Source/PC metric to include only the significant source vectors did not significantly alter symptom prediction compared to the model with all originally identified source vectors, as evaluated by chi-square comparisons of full and nested model likelihood statistics. A statistically nonsignificant result (i.e., a small value for the chi-square) indicates the nested model gives relatively the same fit as the full model. For the Irritancy/PC metric, a comparison of the ability to predict SBS symptoms with all 4 source vectors of the Irritancy/PC metric (full model) versus the ability of a reduced model to predict SBS symptoms with 2 source vectors of the Irritancy/PC metric (nested model) showed no significant changes ($p > 0.3$). Similarly, for the Source/PC metric, the ability of the reduced model to predict SBS symptoms with only 1 source vector compared to all 4 source vectors showed no significant changes ($p > 0.1$). As exposure metrics with only 2 and 1 source vector(s) (Irritancy/PC and Source/PC metrics, respectively) predicted symptoms relatively well, the simpler exposure metrics were retained.

Table 34 presents the results of the chi-square comparisons for the Irritancy/PC and Source/PC metrics. Symptoms for which the Irritancy/PC metric showed significant correlations ($p < 0.05$) included: eye, skin, irritant, stuffy nose, sleepiness, overall, and irritant mucous membrane. The Source/PC metric was significant for only two nasal symptoms (stuffy nose and irritated mucous membrane symptoms, $p < 0.05$).

Crude ORs and 95% confidence intervals (95% CI) for the Irritancy/PC metric sources are presented in Table 35. Crude ORs of the water-based paints and solvents source were

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TABLE 34. Irritancy/PC and Source/PC Metrics in an adjusted model: Chi-square comparisons of maximum log-likelihood estimations, with and without metrics[a]

Symptom	Irritancy/PC X^2	$p <$	N	Source/PC X^2	$p <$	N
Eye	12	0.003	403	1.7	0.19	403
Skin	9.2	0.01	395	2.3	0.13	395
Throat	5.1	0.08	395	2.3	0.13	395
Irritant	13	0.002	416	1.7	0.19	416
Chest Tightness	2.2	0.33	350	0.2	0.65	350
Difficulty Breathing	0.4	0.82	373	0.0	0.83	373
Runny Nose	4.3	0.12	404	1.8	0.18	404
Stuffy Nose	6.6	0.04	395	6.3	0.01	395
Sleepiness	11	0.01	386	3.5	0.06	386
Fatigue	2.5	0.28	403	0.0	0.87	403
Headache	2.2	0.34	399	0.1	0.83	399
Overall	11	0.004	425	1.5	0.22	425
Irritated Mucous Membrane	14	0.001	419	5.1	0.02	419
Ear	!			!		
Shoulder	3.1	0.21	392	0.3	0.55	392
Tooth	!			!		

a. "!" indicates maximum likelihood statistics could not be estimated.

significant for all variables (CIs excluded 1.0), except for fatigue and the non-SBS symptoms (ear, shoulder, tooth). Crude ORs for the carpet/building materials source hovered near 1.0 and were not significant (CIs included 1.0), except for the eye symptom.

Adjusted ORs for the water-based paints and solvents source were also presented in Table 35. With adjustment, ORs were elevated above the crude ORs and again statistically significant (CIs excluded 1.0) for eye (OR=1.7), skin (OR=2.2), throat (OR=1.8), irritant (OR=1.8), stuffy nose (OR=1.7), sleepiness (OR=1.6), overall (OR=1.8), and irritated mucous membrane (OR=1.8) symptoms. ORs for the carpet/building materials source were less significant; after adjustment, only the eye, irritant, sleepiness, and irritated

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TABLE 35. Crude and adjusted ORs for statistically significant vectors of the Irritancy/PC Metric[a]

Symptom	Water-based Paints and Solvents Source				Carpet/Building Materials Source			
	Crude		Adjusted		Crude		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Eye	1.3	1.0-1.7	1.7	1.1-2.7	1.2	1.0-1.5	1.6	1.1-2.4
Skin	1.6	1.1-2.2	2.2	1.3-3.7	1.2	0.9-1.5	1.2	0.7-2.0
Throat	1.3	1.0-1.8	1.8	1.1-3.1	0.9	0.7-1.1	0.9	0.6-1.4
Irritant	1.3	1.0-1.6	1.8	1.2-2.7	1.1	0.9-1.3	1.4	1.0-1.9
Chest Tightness	1.6	1.0-2.6	1.8	0.8-4.0	0.9	0.6-1.3	0.9	0.4-1.8
Difficulty Breathing	1.5	1.0-2.3	1.2	0.5-2.7	0.9	0.7-1.3	1.2	0.5-2.6
Runny Nose	1.5	1.0-2.0	1.6	0.9-2.8	1.0	0.8-1.3	1.3	0.8-2.1
Stuffy Nose	1.5	1.1-2.0	1.7	1.1-2.8	0.9	0.8-1.2	1.3	0.8-2.0
Sleepiness	1.6	1.2-2.1	1.6	1.0-2.4	1.1	0.9-1.4	1.5	1.0-2.1
Fatigue	1.2	0.9-1.5	1.3	0.9-2.0	1.0	0.8-1.2	1.1	0.8-1.6
Headache	1.4	1.0-2.0	1.4	0.8-2.3	1.1	0.8-1.4	1.2	0.8-1.9
Overall	1.7	1.3-2.2	1.8	1.2-2.7	1.1	0.9-1.3	1.1	0.8-1.5
Irritated Mucous Membrane	1.4	1.1-1.8	1.8	1.2-2.7	1.1	0.9-1.3	1.4	1.0-1.9
Ear	1.2	0.5-2.7		!	1.0	0.5-1.8		!
Shoulder	1.1	0.8-1.6	1.7	0.9-3.2	1.0	0.7-1.3	0.9	0.6-1.7
Tooth	1.5	0.5-4.5		!	0.6	0.3-1.4		!

a. "!" indicates maximum likelihood statistics could not be estimated.

mucous membrane systems had ORs slightly elevated above crude OR and statistically significant (CIs excluded 1.0).

Crude ORs and 95% confidence intervals (95% CI) for the Source/PC metric vector (cleaning source) are presented in Table 36 . Although small, ORs of the cleaning source were significant (ORs were above 1.0) for all but the chest, ear and tooth symptoms. Adjusted ORs for the cleaning source were not significant, except for the stuffy nose, sleepiness and irritated mucous membrane symptoms.

TABLE 36. Crude and adjusted ORs for the statistically significant vector of the Source/PC metric[a]

| Symptom | Cleaning Source | | | |
| | Crude | | Adjusted | |
	OR	95% CI	OR	95% CI
Eye	1.3	1.1-1.7	1.3	0.9-1.8
Skin	1.3	1.0-1.6	1.4	0.9-2.1
Throat	1.5	1.2-1.9	1.3	0.9-2.0
Irritant	1.3	1.0-1.6	1.2	0.9-1.7
Chest Tightness	1.2	0.8-1.9	0.9	0.5-1.6
Difficulty Breathing	1.4	1.0-2.0	0.9	0.5-1.6
Runny Nose	1.4	1.0-1.8	1.3	0.9-2.1
Stuffy Nose	1.5	1.2-1.9	1.6	1.1-2.4
Sleepiness	1.3	1.1-1.6	1.4	1.0-1.9
Fatigue	1.3	1.0-1.5	1.0	0.7-1.3
Headache	1.3	1.0-1.6	1.0	0.7-1.6
Overall	1.2	1.0-1.5	1.2	0.9-1.6
Irritated Mucous Membrane	1.4	1.2-1.7	1.4	1.0-1.9
Ear	0.9	0.5-1.8	1.2	0.7-1.8
Shoulder	1.3	1.0-1.8	1.3	0.9-1.8
Tooth	2.3	0.9-5.8	!	

a. "!" indicates maximum likelihood statistics could not be estimated.

Goodness of Fit

The fit was assessed by chi-square comparison of the observed outcomes versus those predicted by the adjusted model over 10 deciles of risk, as described by Selvin (1982) (Appendix H). A statistically nonsignificant result indicates no strong evidence for the lack of fit (i.e., a small value for the chi-square). Chi-square comparisons for most symptoms using the Irritancy/PC indicated the fit was good ($0.9 > p > 0.32$); the fit was less good for the fatigue ($p > 0.1$) symptom. For the Source/PC metric, the fit was relatively good ($0.9 > p > 0.12$).

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Implications of Results

For the logistic regression model, the effect of the multiple independent variables upon

symptom outcome is described using the odds ratio, which reflects the multiplicative

increase in risk for a *one unit* change in the risk factor (Selvin, 1982). The odds ratio

associated with a single risk factor is the odds given the independent variable versus the

odds without that risk factor, or:

$$\frac{Odds_1}{Odds_0} = \frac{\pi(x=1)}{\pi(x=0)} = \frac{e^{(\beta_0 + \beta_1 \times 1)}}{e^{(\beta_0 + \beta_1 \times 0)}} = e^{\beta_1} . \qquad \text{(EQ 3)}$$

Therefore, the odds ratio associated with a specific risk factor is e^β, where the regression

coefficient (β) reflects the adjusted association (accounting for the influence of the other

risk factors and confounders) between the independent variable and the outcome. Further,

the risk of experiencing a symptom is elevated for each t unit increase of β, $((e^\beta))^t$, or,

$e^{\beta t}$. A small β can have a significant influence on the risk, dependent upon the variation in

VOC concentration levels experienced by individuals in office settings.

Note that although the principal component source vectors are developed based on VOC

concentrations experienced in the California buildings, the vectors are not in concentration

(ppb) units. Principal component analysis iteratively developed coefficients for each VOC

which reflect the association (positive or negative) of that VOC with each principal

component. The principal components (representative of identified sources) are composed

of the sum of original VOC concentrations multiplied by the principal component

coefficients estimated for each VOC; these sums range from roughly -5 to 3. For the

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water-based paints and solvents source, the reported ORs represent the increased odds of experiencing the symptoms given a one unit change in the principal component (where the range is -2 to 3). Therefore, it is the increase in VOC exposure that results in a one unit change in the principal component that will increase the odds of observing SBS symptoms. As TVOC levels of 1 mg m^{-3} or greater have been reported to be positively associated with irritant symptoms, it is likely that increased VOC exposure of 1 mg m^{-3} could cause the increase in the odds of experiencing SBS symptoms of irritation.

For example, the largest regression coefficient for the water-based paints and solvents source was the coefficient for the skin symptom (β =0.79). Therefore, the increase in VOC concentration resulting in a 2 *unit* increase in the water-based paints and solvents source would represent an increase in the odds of experiencing skin irritation from OR=2.2 to OR = 4.9 ($OR = e^{0.79x2} = e^{1.6} = 4.9$). The odds of experiencing irritated mucous membrane would similarly increase to OR=3.2 with a 2 unit increase in the water-based paints and solvents source (from OR=1.8).

Discussion

In this study several new metrics of VOC exposure were developed and tested with respect to their influence on the expression of adverse health outcomes measured by self-reported SBS irritancy symptoms. Chi-square comparisons of models with and without VOC exposure metrics were used to evaluate the influence of 7 different metrics on individual and composite symptoms. Two of the exposure metrics, the Irritancy/PC metric

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and the Source/PC metric, were statistically significant in a model of symptom prediction; the Irritancy/PC metric had greater statistical power than any of the other VOC exposure metrics. This metric was driven mainly by the water-based paints and solvents source. The more typical VOC exposure metrics used in prior analyses were not useful in symptom prediction in the logistic model (TVOC, ΣVOC_i). Also not useful were the VOC metrics that took into account potency, but did not adjust for the highly correlated nature of the data set, or the presence of VOCs that were not measured (Irritancy/ΣVOC_i, Odor/ΣVOC_i, Chemical Class). The Source/PC metric was useful in a model with all cases, which included TVOC levels elevated (> 2 mg m^{-3}) due to the presence of liquid-process photocopiers. None of the adjusted metrics were useful in the prediction of shoulder pain or numbness (one of the symptoms used to represent over-reporting). Logistic regression estimates of the impact of earache and toothache would not converge, due to the low number of symptoms reported.

Eye Irritation

For eye irritation, the results reflected by the adjusted ORs of the Irritancy/PC metric with and without high TVOC values were especially noteworthy. Adjusted ORs for the individual sources of the Irritancy/PC metric indicated that the water-based paints and solvents source could account for a significant proportion of the observed association of symptoms with this metric. For symptoms related to eye irritation, adjusted ORs for the water-based paints and solvents source were elevated and statistically significant: 1.7

(95% CI 1.1 - 2.7), 1.8 (95% CI 1.2-2.7), and 1.8 (95% CI 1.2 - 2.7), for eye, irritant, and irritated mucous membrane symptoms, respectively.

Elevated TVOC concentrations were measured in two buildings with liquid process photocopiers. TVOC levels in these buildings were 2 to 7 mg m^{-3}, compared to a median value of 0.5 mg m^{-3} when high TVOC values were excluded. Fifty-seven subjects were located at these sites; 42 and 15 individuals were located in buildings 4 and 5.6, respectively. The influence of high TVOC concentrations on the Irritancy/PC and Source/PC metrics was evaluated by removing individuals with high TVOC exposures; the results are presented in Table 37. Even with high TVOC exposures excluded, the Irritancy/PC

TABLE 37. Influence of high TVOC: Chi-square change for Irritancy/PC and Source/PC metrics on subset of data where high TVOC cases have been removed

| | High TVOC Cases Removed | | | |
| | Irritancy/PC | | Source/PC | |
Symptom	x^2	$p <$	x^2	$p <$
Eye	7.3	0.03	0.1	0.73
Skin	8.4	0.02	1.0	0.31
Throat	3.8	0.15	2.5	0.12
Irritant	8.7	0.01	0.4	0.52
Chest Tightness	2.2	0.34	0.2	0.68
Difficulty Breathing	0.3	0.85	0.2	0.68
Runny Nose	2.0	0.37	0.4	0.51
Stuffy Nose	6.0	0.05	3.3	0.07
Sleepiness	6.5	0.04	1.0	0.32
Fatigue	0.9	0.65	0.8	0.37
Headache	0.8	0.69	0.2	0.68
Overall	7.8	0.02	0.0	0.98
Irritated Mucous Membrane	11	0.004	2.9	0.09

metric was statistically significant in the prediction of irritancy symptoms. Exclusion of

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11% of the cases (n=57) slightly decreased the usefulness of the adjusted Irritancy/PC metric with all cases versus the usefulness of the Irritancy/PC metric with high TVOC sites removed for eye ($p < 0.003$ vs. $p < 0.03$), irritant ($p < 0.002$ vs. $p < 0.01$), and irritated mucous membrane ($p < 0.004$ vs. $p < 0.001$) symptoms[1]. By comparison, the usefulness of the Source/PC metric decreased to non significance ($p < 0.05$).

Analysis from the current study on California buildings has indicated that VOCs from liquid-process photocopiers contribute to symptoms of mucosal irritation. The source of the elevated TVOC concentrations observed in this study were VOCs of high molecular weight emitted by liquid-process photocopiers. The gas chromatograms of the air samples from these sites were dominated by a mixture of C_{10}-C_{11} isoparaffinic hydrocarbons characteristic of these photocopiers. In chamber experiments with 63 healthy subjects exposed to *n*-decane (C_{10}), significant decreases in tear film stability were observed with exposures of 6 to 20 mg m^{-3} over 6 hours (Kjaergaard et al., 1989). High TVOC concentrations found in CHBS approached the concentrations observed to cause eye irritation in the chamber study, although the alkanes were not identical; TVOC levels for CHBS Buildings 4 and 5.6 were 2 and 7 mg m^{-3}, respectively. Kjaergaard et al.'s study provides evidence from a controlled chamber exposure experiment that is consistent with the observed impact of high TVOC sites on the adjusted model of eye irritation for the CHBS field study.

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1. Note that the "irritant" and "irritated mucous membrane" variables focus on different groups of symptoms. The irritant symptom variable was composed of eye, skin, or throat symptoms. The irritated mucus membrane variable was composed of eye, throat, runny nose, or stuffy nose symptoms.

Skin Irritation

The association of the adjusted Irritancy/PC metric with skin symptoms was also

noteworthy. The change in likelihood values between nested logistic regression models,

with and without the Irritancy/PC metric, approximates a chi-square distribution. As the

adjusted OR for the carpet/building materials source is small and nonsignificant (OR=1.2,

95% CI 0.7-2.0), the large and statistically significant chi-square change in the model of

skin irritation due to removal of the Irritancy/PC metric (χ^2=9.2, p < 0.01) is likely to be

driven by the water-based paints and solvents source (OR=2.2, 95% CI 1.3-3.7).

Additionally, upon removal of the high TVOC sites, the significance of all chi-square

changes was reduced; however, even for the subset of data without high TVOC sites, the

strength of the association between the adjusted Irritancy/PC metric and the skin symptom

was almost unchanged (χ^2=8.4, p < 0.02). By comparison, for the subset without high

TVOC sites the association between the adjusted Source/PC metric and skin symptoms

was effectively eliminated (χ^2=1.0, p < 0.31). These results suggested the Irritancy/PC

metric measured, or in some way took into account, the VOC(s) that caused dermal

irritation.

To investigate the potential influence of the Irritancy/PC metric on skin irritation, the two

principal component vectors were plotted versus building and site location. No pattern

was observed for the carpet/building materials vector. However, as seen in Figure 15, a

plot of the water-based solvents and paints vector versus building and site location

identified two sites where the vectors were elevated, 11 and 71, in buildings 1 and 7,

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FIGURE 15. Water-based Paints and Solvents Vector by Location (Spaces within Buildings)
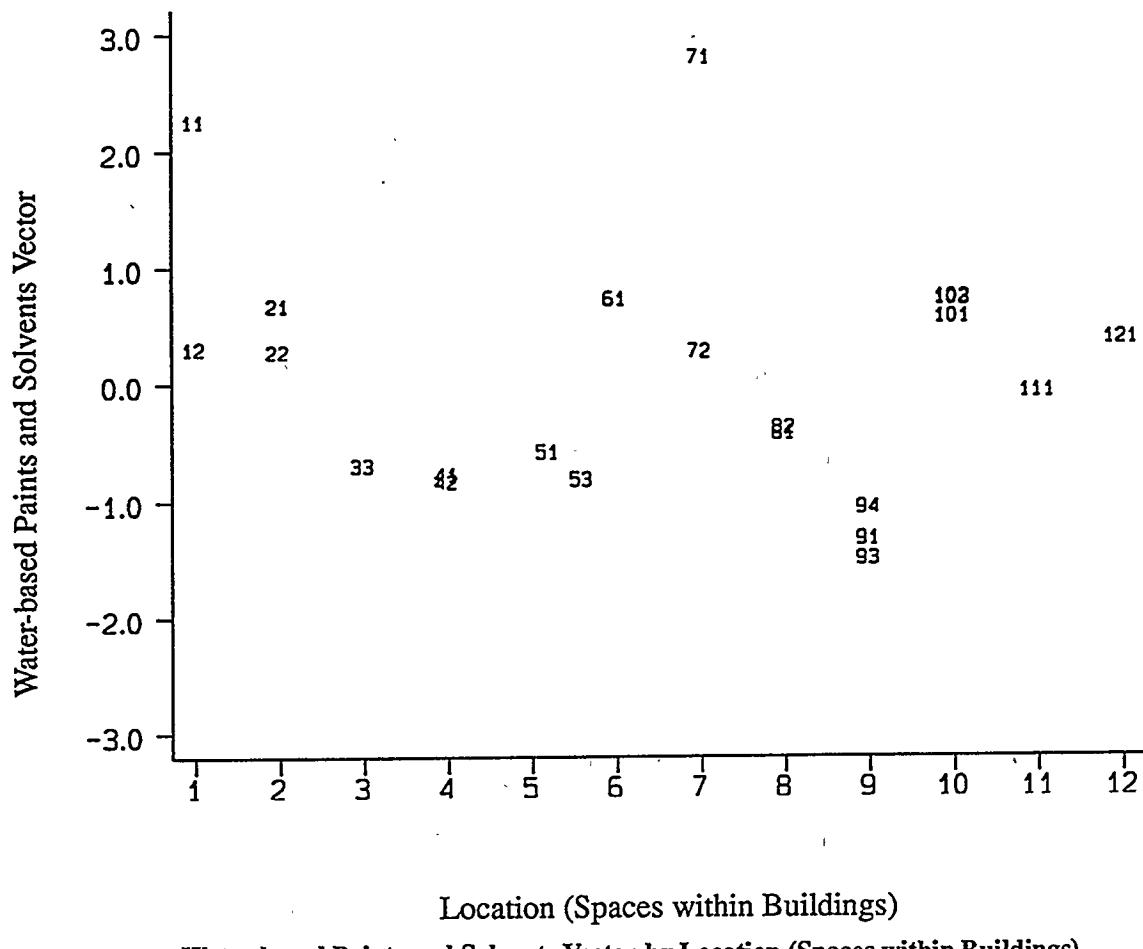
respectively. A total of 29 individuals were located in space 11 (n=11) and 71 (n=18).

Elevated levels of the water-based paints and solvents source found in these two locations

appeared to be the cause of the observed relationship between the Irritancy/PC metric and

the skin symptom. The chi-square comparison between full and nested models with all

sites (N=395) was 9.2 (p < 0.01). Upon removal of the individuals located in two sites

with high vectors (n=29), the chi-square comparison was 2.8 (p < 0.24).

A possible explanation for this finding was that only the measured 2-butoxyethanol, the main VOC driving this vector, was the cause of the observed relationship. The maximum (27 ppb) and next most elevated (6 ppb)[1] concentrations of 2-butoxyethanol were observed for space 11 and 71, respectively. This hypothesis was tested by replacement of the Irritancy/PC metric in the logistic regression model with the variable representing 2-butoxyethanol. The results indicated that this individual VOC did not predict the skin symptom. The use of 2-butoxyethanol alone in the model was nonsignificant when evaluated by either the compound's regression coefficient ($p < 0.23$), or by the chi-square change when the compound was removed from the model ($p < 0.24$). This analysis supported the hypothesis that 2-butoxyethanol was a tracer for water-based paints and solvents, a set of compounds known to cause dermal irritation.

Exposures to Water-based Paints and Solvents

Water-based paints and solvents have replaced white spirit and other organic solvents due to the adverse health impacts (brain damage) of the latter. However, irritant symptoms (eye, nose and throat, headache) due to occupational exposures of water-based paints and solvents containing 2-butoxyethanol and other glycol ethers have been reported in a comprehensive review of toxicological studies (Hansen et al., 1987). Field studies have implicated water-based paints and solvents or their constituent compounds in lung function changes (Ware et al., 1993; Wieslander et al., 1994).

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1. In two other spaces (61 and 82), 2-butoxyethanol was also at 6 ppb.

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2-Butoxyethanol is rapidly absorbed by the human body through both respiration (Johanson et al., 1986) and dermal exposure (Johanson and Boman, 1991). Glycol ethers in the blood stream are primarily converted to alkoxyacetic acid metabolites, which can be measured in the urine (Johanson et al., 1986). Researchers reported that dermal uptake of 2-butoxyethanol, as measured by blood and urine concentrations, accounted for 75% (45-85%) of the total uptake during whole body exposure to 2-butoxyethanol vapor in a chamber experiment (Johanson and Boman, 1991).

The potential for significant contribution to overall exposure by the dermal route (including mucous membranes and the eyes) during occupational activities has been recognized by the ACGIH. The 2-butoxyethanol TWA includes a "skin" notation, which is "... intended to alert the reader that air sampling alone is insufficient to accurately quantitate exposure..." (American Conference of Governmental Industrial Hygienists, 1992). The importance of the dermal route for other glycol ethers/acetates is indicated by the same skin designation for other compounds reported by Hansen et al. (1987) to be in water-based paints or solvents (e.g., ethylene glycol ethyl ether (2-ethoxyethanol), ethylene glycol ethyl ether acetate (2-ethoxyethyl acetate), ethylene glycol methyl ether (2-methoxyethanol), dipropylene glycol methyl ether, etc.).

Vincent et al. (1990) evaluated occupational exposures of 16 cleaning women and 13 car cleaners to 2-butoxyethanol by environmental and biological monitoring. Environmental measurements of 2-butoxyethanol included samples of the window cleaning agent used, and air samples in the workers' breathing zone (TWA); samples were analyzed by GC-MS

for 2-butoxyethanol concentration. Urine samples were taken for all workers, and urinary concentrations of 2-butoxyethanol metabolite butoxyacetic acid were determined. The correlation between air concentrations of 2-butoxyethanol and urinary butoxyacetic acid was significant (p<0.01) but low (r=0.60). By comparison, the correlation between urinary butoxyacetic acid and estimated daily quantity of window cleaning agent used per worker was extremely high (r=0.96) and significant (p < 0.01). Exposure assessment included a questionnaire filled out by each worker regarding work practices; the majority of workers did not use protective gloves. Due to the smaller correlation between air samples of 2-butoxyethanol and the urinary metabolite of 2-butoxyethanol, and due to the knowledge of work practices, the researchers hypothesized that dermal exposure was predominant.

In a case-control study of house painters, Wieslander et al. (1994) reported occupational exposures to water-based paints containing glycol ethers were related to eye and skin irritation. Controls included male dairy workers and male packers in private pulp industries; for controls, occupational exposures to dust and VOCs were 0.2 mg m^{-3} and 0.5 mg m^{-3}, respectively. For 8 cases (painters), the average 8-hour occupational exposure to volatile organic compounds in various brands of water-based paints was 2.1 mg m^{-3}, with a range of 0.7 - 4.9 mg m^{-3}. ORs for exposed house painters were elevated compared to non-exposed controls for eye irritation (OR=1.7, 95% CI 1.03-2.7) and itching on the hands (OR=1.9, 95% CI 1.1-3.3). These exposures and results are consistent with the VOC measurements and ORs reported in this study of California office workers. Average (arithmetic) TVOC levels in workplace air for the California study were 0.9 mg m^{-3}, with

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a range of 0.2 - 7 mg m^{-3}. Adjusted ORs for the water-based paints and solvents source were 1.7 for eye symptom (95% CI, 1.1-2.7) and 2.2 for skin symptom (95% CI, 1.3-3.7) for the office workers in the CHB study. Additionally, the Swedish researchers found the number of years working as a painter exposed to water-based paints was related to a decrease in FEV, although not to the degree found with solvent based paints. In the CHB study the water-based paints and solvents vector gave a relatively high adjusted OR for chest tightness (OR = 1.8), although the relationship was not significant (CI 95% 0.5 - 2.7).

Limitations of the Study

Potentially important sensory irritants were not measured in the CHBS study. Environmental measurements were not available for formaldehyde or ozone. Attempts were made to sample formaldehyde; however, the sampling system failed. Ozone was not targeted for sampling.

Ozone is a strong irritant, and is one of the six ambient compounds for which there are National Ambient Air Quality Standards (NAAQSs). The maximum daily 1-hour average NAAQS for ozone is 0.12 ppm (235 ug m^{-3}). Acute health effects (reduced lung function) in children have been reported for exposures experienced at summer camp, where the highest 1-hour ozone level was 0.15 ppm (Spektor et al., 1991). Chronic health effects (changed forced expiratory velocity (FEV)) have been observed in healthy adult men exposed in a chamber experiment; exposures of 0.12 ppm ozone for 6.6 hours for 5 consecutive days showed changed FEV (-12.79, -8.73, -2.54, -0.6, +0.18%, respectively)

(Folinsbee et al., 1994). During the period of sampling for the California buildings, the ambient ozone values were extremely low (0.14 - 0.48 ppb) (Bay Area Air Quality Management District, 1994), although potential indoor sources of ozone were known to be present in the CHBS buildings (photocopiers).

Formaldehyde commonly is found indoors, and the irritant effects of the compound have been well documented; eye and respiratory tract irritation generally occurs at levels of 1 mg m^{-3} (1 ppm) (World Health Organization, 1989). Clean tropospheric and polluted urban air concentrations of formaldehyde have been reported at 0.4 ppb and 20-50 pbb, respectively (Seinfeld, 1986). Therefore, even polluted urban air concentrations of formaldehyde are typically an order of magnitude below the concentrations required to cause irritant symptoms. However, indoor levels of formaldehyde may have been elevated enough to cause or contribute to irritant eye and skin symptoms.

Lack of indoor measurements of formaldehyde, ozone, or other potentially irritating pollutants may have been partially compensated for by the ability of the principal component analysis to identify sources of a group of compounds through a single or few tracers. Formaldehyde has been found in tobacco smoke, automobile emissions, materials used in buildings and home furnishings, and in consumer and medicinal products (World Health Organization, 1989). As the buildings chosen were non-smoking, and two formaldehyde sources (automobile emissions and building materials) were identified in the principal component analysis, some impact of the formaldehyde may have been taken into account by the use of principal component analysis.

Conclusions

New metrics of VOC exposure, developed using an integrated, relative irritancy scale and adjusted for the highly correlated nature of the VOC mixture by means of principal component analysis, predicted individual and composite SBS symptoms in a cross-sectional study of office buildings for which total VOC concentrations were generally less than 0.5 mg m^{-3}. The Irritancy/PC metric correlated significantly ($p < 0.05$ or $p < 0.001$) with work-related symptoms of eye, skin, irritant, stuffy nose, sleepiness, overall, and irritated mucous membrane symptoms. Four source related vectors were identified by the Irritancy/PC metric: motor vehicle emissions, building materials, carpet/building materials, and water-based paints and solvents. One of the source related vectors accounted for most of the usefulness of the Irritancy/PC metric, the water-based paints and solvents source. This vector was also significantly useful in a model of dermal irritation as evaluated by the dry, irritated or itching skin symptom. For a relatively small set of cases, the vector representing this source had high levels. Removal of these cases eliminated the observed correlation between the water-based paints and solvents source and skin symptom.

The buildings of the CHBS study were chosen without regard to problem building status, and in general TVOC levels were low. The median TVOC level was 0.46 mg m^{-3}, excluding high TVOC sites. However, TVOC concentrations impacted by the presence of liquid-process photocopiers (2 to 7 mg m^{-3}) were within the range TVOC levels reported to cause symptoms in chamber experiments and TVOC levels reported in complaint

buildings, 1 - 25 mg m^{-3} and 1 - 5 mg m^{-3}, respectively. Analyses demonstrated that high TVOC levels impacted both Irritancy/PC and Source/PC metrics in an adjusted model; removal of the cases with high TVOC levels slightly reduced the power of the Irritancy/ PC metric, and eliminated the ability of the Source/PC metric to predict irritancy symptoms. The CHBS buildings were chosen to be representative of the typical office environment. Selection requirements specifically excluded buildings with unusual pollutant sources, or ongoing renovations. Therefore, the results from the current study suggest that for a wider range of pollutant exposures, stronger correlations might be observed between irritant symptoms and VOC exposure metrics based on irritancy and principal component analysis. The approach developed herein takes into account potency as well as the highly correlated nature of the data set, and should be applicable to other office settings.

Appendices

Appendix D Principal Component Analysis

$$\text{Principal Component} = P_k^{(j)} = \left(\sum_{i=1}^{n} a_{ij} X_{ik} \right) \qquad \text{(EQ 4)}$$

where:

$P_k^{(j)} =$ j^{th} principal component for the kth case;

$X_{ik} =$ standardized value of the ith variable for case k;

$a_{ij} =$ principal score coefficient for the ith variable and the jth principal component;

$n =$ number of variables in principal component analysis.

Principal component analysis was run using Stata 3.1. Principal components were calculated based on the correlation matrix; the technique standardizes all variables (i.e., mean 0, standard deviation 1). The covariance matrix was considered, as VOC units are all ppb; however, as the geometric means for some compounds were large (GM > 3), the standardized variable set was deemed more appropriate. (See Appendix I for more detail on principal components calculated for this study.)

Appendix E Multivariate Logistic Regression Analysis

Research has indicated that SBS is multifactorial in origin, i.e., several different risks

factors including VOC exposure are believed to influence symptoms. Multivariate logistic

regression has become the standard method to model the relationship between adverse

health outcomes and numerous independent variables. Multivariate logistic regression

analysis differs from typical regression analysis in that the outcome is dichotomous or

binary; the dependent variable of interest is the presence or absence of an adverse health

outcome. The properties of this technique allow modeling of the risk, or probability, of an

adverse outcome based on continuous and categorical independent variables. The logistic

transformation is often used for the analysis of dichotomous outcome variables both

because it is flexible mathematically and because it allows for biologically meaningful

interpretation (Hosmer and Lemeshow, 1989).

The logistic regression model derives from the mathematical function (Kleinbaum et al.,

1982):

$$f(y) = \frac{1}{1 + e^{-(y)}} \tag{EQ 5}$$

where:

$0 < f(y) < 1$ = the outcome is bound by zero and 1;

$-\infty < y < +\infty$ = the variable is unbound;

and where y can be a function of k independent variables:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 \ldots + \beta_k x_k ; \tag{EQ 6}$$

where:

x_i = independent variables;

β_i = coefficients of the independent variables estimated from the data.

The probability of symptom occurrence is estimated by considering the probability of an event versus the probability of no event, or

$$Odds = \frac{Probability\,(event)}{Probability\,(no\;event)},\qquad\text{(EQ 7)}$$

and since

$$Probability\,(no\;event) = 1 - Probability\,(event),\qquad\text{(EQ 8)}$$

then

$$Odds = \frac{Probability\,(event)}{1 - Probability\,(event)}.\qquad\text{(EQ 9)}$$

The *probability* of occurrence of outcome given independent variable x can be represented by $\pi(x)$. Placing this into the context of the previous equation gives in symbols:

$$Odds = \frac{\pi(x)}{1 - \pi(x)}.\qquad\text{(EQ 10)}$$

Combining the mathematical function of the logistic function with the notation for probability gives $\pi(x) = \frac{1}{1 + e^{-(y)}}$, and the probability of no event is accordingly

$1 - \pi(x) = 1 - \frac{1}{1 + e^{-(y)}}$. Therefore, the odds is equivalent to:

$$Odds = \frac{\pi(x)}{1 - \pi(x)} = \frac{\dfrac{1}{1 + e^{-(y)}}}{1 - \dfrac{1}{1 + e^{-(y)}}} = \frac{1}{e^{-y}} = e^{y}.\qquad\text{(EQ 11)}$$

As y can be expressed as a function of k independent variables then the symptom outcome as predicted by multiple independent variables is:

$$Odds = \frac{\pi(x)}{1 - \pi(x)} = e^{(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k)} . \qquad \text{(EQ 12)}$$

When there is difficulty in interpretation, a typical technique used in statistical analysis is transformation of the data. The odds of observing the outcome is transformed by taking the natural log of both sides of the equation. Transformation of $\frac{\pi(x)}{1 - \pi(x)}$ to $\ln\left[\frac{\pi(x)}{1 - \pi(x)}\right]$ results in an function termed the *log-odds*. As compared to $\pi(x)$ and $\frac{\pi(x)}{1 - \pi(x)}$, the log-odds is bound by $-\infty$ and $+\infty$.

Using the log transformation on Equation 12 to achieve linearity in x gives:

$$Log\text{-}Odds = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 \dots + \beta_k x_k \qquad \text{(EQ 13)}$$

where:

Odds =	likelihood of experiencing the symptom outcome for a one unit increase in change of the independent variable(s),
Log-Odds =	natural log of the odds,
β_i =	coefficients of the independent variables estimated from the data, and
x_i =	independent variables (VOC metrics and other variables).

Appendix F The Odds Ratio

For the logistic regression model, the effect of the multiple independent variables upon symptom outcome is described using the odds ratio, which reflects the multiplicative increase in risk for a *one unit* change in the risk factor (Selvin, 1982). The odds ratio associated with a single risk factor is the odds given the independent variable versus the odds without that risk factor, or:

$$\frac{Odds_1}{Odds_0} = \frac{\pi(x=1)}{\pi(x=0)} = \frac{e^{(\beta_0 + \beta_1 \times 1)}}{e^{(\beta_0 + \beta_1 \times 0)}} = e^{\beta_1}. \qquad \text{(EQ 14)}$$

Therefore, the odds ratio associated with a specific risk factor is e^{β}, where the regression coefficient (β) reflects the adjusted association (accounting for the influence of the other risk factors and confounders) between the independent variable and the outcome.

Further, the risk of experiencing a symptom is elevated for each t unit increase of β, $((e^{\beta}))^t$, or, $e^{\beta t}$. A small β will be a significant influence on the increase in odds with the risk factor, dependent upon the variation in ppb levels experienced by individuals in office settings.

Appendix G Maximum Likelihood Estimation and The Likelihood Ratio Test

As described by Kleinbaum et al. (1982), maximum likelihood (ML) estimation chooses estimators (β coefficients) of the parameters in a likelihood function that maximizes the value of the function. Assume that $L \equiv L(\theta)$ represents a likelihood function involving a vector of parameters θ; the parametric vector θ includes all beta coefficients and constants for the risk factors in the model. The ML estimator of θ is defined to be that unique vector θ of numerical functions of the observed data for which $L(\theta)$ is a maximum. Maximizing $L(\theta)$ is equivalent to mazimizing the more mathematically tractable $\ln L(\theta)$, therefore, the elements of θ are usually found by setting the partial derivative of $\ln L(\theta)$ with respect to each θ equal to zero, and iteratively solving for the maximum value of $\ln L(\theta)$.

The likelihood function represents the probability of observing the data obtained as a function of the unknown parameters. The parameters estimated by the ML estimation agree most closely with the data actually encountered. The importance of the parameters estimated is tested using the likelihood ratio test.

The importance of the VOC metrics (and other risk factors) are evaluated by comparing ratios of two log-likelihood functions. The difference between the log-likelihood statistics for two models, one of which is nested in the other, approximates a chi-square distribution in large samples[1]. The χ^2 likelihood ratio test is performed between pairs of log-likelihood functions after model estimation, in this case by logistic regression. The full model

---

1. This test is analogous to the F-test in typical multivariate regression, used to assess the importance of a group of variables to the regression model.

includes all variables, while the reduced model lacks the variables whose influence is

being tested, i.e., the VOC metrics.

$$\chi^2 = -2 \cdot (L_1 - L_0)_{df = d_0 - d_1} \qquad \text{(EQ 15)}$$

where:

$\chi^2 =$ chi-square test of differences between full and constrained log-likelihood models (with $d_0 - d_1$ degrees of freedom);

$L_0 =$ log-likelihood value associated with the full model (with d_0 degrees of freedom);

$L_1 =$ log-likelihood value associated with the constrained model (with d_1 degrees of freedom).

Appendix H Deciles of Risk

The independent variables are entered into Equation 12 to predict symptom outcome. The fit of the model can be assessed by compared the observed outcomes versus those predicted by the equation. A standard chi-square test of the observed versus expected pattern gives a basic measure of fit. A fuller assessment can be accomplished by considering the fit over various levels of risk. As discussed by Selvin (1982):

> "One strategy uses categories based on levels of risk estimated from the logistic model under consideration. Traditionally, ten groups are formed, each containing approximately one-tenth of the data. The members of the first group are all subjects with the lowest probability of the event estimated by the logistic model, while the second group makes up the next 10% of the subjects with respect to risk and so forth" ... "The percentile groups are sometimes called 'deciles of risk.'"

After the deciles of risk are formed, the average logistic probability per decile can be calculated (from Selvin, 1982):

$$\bar{p}_k = \frac{1}{n_k} \cdot \sum_{j=1}^{n_k} p_j \qquad \text{(EQ 16)}$$

where:

$k =$ number of deciles;

$\bar{p}_k =$ probability of outcome per decile;

$p_j =$ estimated probability of outcome based on the estimated regression coefficients;

$n_k =$ number of cases in each decile.

The expected number of events in each decile can be calculated by $e_k = nk \times \bar{p}_k$.

A chi-square based on the deciles of risk can then be calculated. The chi-square statistic with eight degrees of freedom is:

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$$\sum_{i=1}^{10} \frac{\left(o_i - e_i\right)^2}{n_i \bar{p}_i \cdot (1 - \bar{p}_i)} \qquad \text{(EQ 17)}$$

The use of deciles of risk not only allows an examination of the fit of the model, but also

indicates where a *lack* of fit occurs. A small value for the chi-square indicates the fit is

good, indicating no strong evidence of the lack of fit of the logistic model (Selvin, 1982).

**Appendix I Sample estimation of principal component analysis and
logistic regression analysis for the Irritancy/PC metric:
Skin symptom**

The following is annotated output from commands used in Stata (version 3.1) that shows
how the principal components were generated from the original VOC measurements, and
how the source vectors identified from this analysis were used in the full, adjusted logistic
regression model for SBS symptoms. Specifically, calculation of the source vectors of the
Irritancy/PC metric (carpet/building materials source and water-based paints and solvents
source) is described in detail, and the use of these source vectors in prediction of the SBS
symptom of skin irritation is shown.

Presented first are the original measurements of 22 VOCs of 10 irritating compounds:
styrene (styrene), ethylacetate (ethylace), butylacetate (butylace), 1,2,4-trimethylbenzene
(v124trim), m/p-xylene (mpxylene), o-xylene (oxylene), n-hexanal (nhexanal), n-pentanal
(npentana), 2-butoxyethanol (v2butoxy), and 2-propanol (v2propa2).

```
. use joann/chbsppb2
.
   spacenum     styrene    ethylace    butylace    v124trim    mpxylene
   1.       11        .49         .58         .31        1.09        2.55
   2.       12        .28         .32         .37         .89        2.28
   3.       21        .35         .75         .39         .57        1.39
   4.       22        .24         .59         .29         .63        1.88
   5.       33        .22         .05         .05         1.1        2.82
   6.       41         .6           3         .05         .37         .95
   7.       42        .66        3.02         .05         .35         .93
   8.       51        .26         .72         .05         .61        1.83
   9.       53        .24        1.33         .05         .64        1.86
  10.       61        .05          .4         .45         .31        2.08
  11.       71        .56          .6         .51        1.23        2.77
  12.       72         .5        1.22         .88        1.16        2.92
  13.       81        .45         .45          .4        1.28        3.55
  14.       82        .47         .43         .39        1.39        3.84
  15.       91        .55         .51         .38        1.64        4.17
  16.       93        .52         .45         .36        1.74        4.61
```

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17.	94	.78	.49	.52	1.65	3.8
18.	101	.67	.11	.38	.54	1.28
19.	102	.7	.13	.32	.53	1.27
20.	103	.6	.05	.32	.5	1.1
21.	111	.87	.1	.05	.8	2.15
22.	121	.66	.07	.18	.64	1.45

. list spacenum oxylene nhexanal npentana v2butoxy v2propa2

	spacenum	oxylene	nhexanal	npentana	v2butoxy	v2propa2
1.	11	.9	.95	.87	27.4	11.2
2.	12	.78	.63	.41	4.68	4.01
3.	21	.52	.56	.36	4.3	1.76
4.	22	.66	.56	.3	3.09	3.02
5.	33	.86	.32	.29	1.28	2.58
6.	41	.32	1.81	1.57	.2	8.15
7.	42	.3	1.92	1.68	.2	7.4
8.	51	.54	.71	.9	.2	.35
9.	53	.6	.1	1.14	.2	.34
10.	61	.56	.72	.96	5.95	.49
11.	71	.88	.49	.05	5.88	61.51
12.	72	.85	.43	.05	1.88	5.21
13.	81	1.09	.41	.1	2.94	6.5
14.	82	1.14	.47	.14	5.55	6.14
15.	91	1.26	.45	.11	1.4	1.68
16.	93	1.36	.32	.05	1.83	1.77
17.	94	1.2	.66	.05	1.15	1.26
18.	101	.43	.4	.05	.2	.1
19.	102	.39	.6	.13	2.47	1.18
20.	103	.39	.47	.05	1.38	.41
21.	111	.65	.3	.05	1.23	5.73
22.	121	.44	.25	.05	.59	2.95

As the geometric mean was greater than 3.0 for some of the VOCs, the principal components were analyzed based on a standardized data set. The standardized (mean 0, variance 1) of the 10 VOCs is presented below.

```
. egen styrens=std(styrene)
. egen ethylacs=std(ethylace)
. egen butylacs=std(butylace)
. egen v124tris=std(v124trim)
. egen mpxylens=std(mpxylene)
. egen oxylens=std(oxylene)
. egen nhexanas=std(nhexanal)
. egen npentans=std(npentana)
. egen v2butoxs=std(v2butoxy)
. egen v2propas=std(v2propa2)
```

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```
. list spacenum styrens ethylacs butylacs v124tris mpxylens
```

	spacenum	styrens	ethylacs	butylacs	v124tris	mpxylens
1.	11	.0131272	-.1444431	.0154708	.4379832	.1910459
2.	12	-.9976614	-.4610004	.3072045	-.0081108	-.0545846
3.	21	-.6607319	.0625367	.404449	-.7218612	-.8642556
4.	22	-1.190192	-.1322679	-.0817739	-.588033	-.4184817
5.	33	-1.286458	-.789733	-1.248709	.4602879	.4366764
6.	41	.5425879	2.801975	-1.248709	-1.167955	-1.264542
7.	42	.8313845	2.826325	-1.248709	-1.212565	-1.282737
8.	51	-1.093927	.0260109	-1.248709	-.6326423	-.4639688
9.	53	-1.190192	.768703	-1.248709	-.5657283	-.4366765
10.	61	-2.104715	-.3635982	.6961827	-1.301783	-.2365332
11.	71	.3500566	-.1200925	.9879164	.750249	.3911894
12.	72	.0612599	.6347749	2.786941	.594116	.5276508
13.	81	-.1794041	-.3027218	.4530714	.8617724	1.100789
14.	82	-.0831385	-.3270723	.404449	1.107124	1.364614
15.	91	.3019239	-.2296701	.3558267	1.664742	1.664829
16.	93	.1575254	-.3027218	.2585822	1.887789	2.065116
17.	94	1.408978	-.2540206	1.036539	1.687046	1.328224
18.	101	.8795173	-.7166813	.3558267	-.7887752	-.9643273
19.	102	1.023916	-.6923308	.064093	-.81108	-.9734247
20.	103	.5425879	-.789733	.064093	-.8779941	-1.128081
21.	111	1.842173	-.7288566	-1.248709	-.2088531	-.172851
22.	121	.8313845	-.7653824	-.6166189	-.5657283	-.809671

```
. list spacenum oxylens nhexanas npentans v2butoxs v2propas
```

	spacenum	oxylens	nhexanas	npentans	v2butoxs	v2propas
1.	11	.5195195	.7534956	.857531	4.214452	.4018491
2.	12	.1468207	.0337386	-.0298119	.2308065	-.1623661
3.	21	-.6606935	-.1237082	-.1262622	.1641787	-.3389286
4.	22	-.225878	-.1237082	-.2420026	-.0479785	-.2400536
5.	33	.3952867	-.663526	-.2612927	-.3653375	-.2745814
6.	41	-1.281858	2.687842	2.207835	-.5547009	.1625088
7.	42	-1.343975	2.935259	2.420026	-.5547009	.1036547
8.	51	-.5985768	.2136778	.9154011	-.5547009	-.4495744
9.	53	-.4122275	-1.158359	1.378363	-.5547009	-.4503592
10.	61	-.5364605	.2361703	1.031142	.4534839	-.4385883
11.	71	.4574031	-.281155	-.7242542	.4412104	4.349786
12.	72	.3642285	-.4161095	-.7242542	-.2601356	-.0681995
13.	81	1.109626	-.4610943	-.6278039	-.0742789	.0330297
14.	82	1.264917	-.3261399	-.5506436	.3833494	.0047797
15.	91	1.637616	-.3711247	-.6085138	-.3442971	-.3452064
16.	93	1.948199	-.663526	-.7242542	-.2689024	-.3381439
17.	94	1.451267	.1012159	-.7242542	-.3881312	-.3781647
18.	101	-.9402175	-.4835867	-.7242542	-.5547009	-.4691925
19.	102	-1.064451	-.0337385	-.5699337	-.1566871	-.3844425
20.	103	-1.064451	-.3261399	-.7242542	-.3478038	-.4448661
21.	111	-.2569364	-.7085108	-.7242542	-.3741043	-.0273939
22.	121	-.9091593	-.8209728	-.7242542	-.4863197	-.2455467

Principal components and principal component coefficients were estimated for 10

irritating VOCs.

```
. factor styrene ethylace butylace v124trim mpxylene oxylene nhexanal
npentana v2butoxy v2propa2,pc
(obs=22)
```

(principal components; 10 components retained)

Component	Eigenvalue	Difference	Proportion	Cumulative
1	4.29315	2.55516	0.4293	0.4293
2	1.73798	0.49665	0.1738	0.6031
3	1.24134	0.11134	0.1241	0.7272
4	1.12999	0.40385	0.1130	0.8402
5	0.72614	0.05575	0.0726	0.9129
6	0.67040	0.53581	0.0670	0.9799
7	0.13459	0.08956	0.0135	0.9934
8	0.04503	0.02812	0.0045	0.9979
9	0.01691	0.01244	0.0017	0.9996
10	0.00447	.	0.0004	1.0000

Between the fourth and fifth principal components, the eigenvalues drop from 1.1 to 0.73.

These four retain 84% of the total variance in the dataset; consequently, only 4 principal

components were retained.

Variable	Eigenvectors 1	2	3	4
styrene	0.03026	0.04230	0.81371	-0.01512
ethylace	-0.32482	0.45684	0.12451	-0.24997
butylace	0.28739	0.09775	0.07875	0.28932
v124trim	0.42350	0.28730	0.06470	-0.22617
mpxylene	0.41775	0.27163	-0.10147	-0.28952
oxylene	0.42125	0.29145	-0.11313	-0.24146
nhexanal	-0.33939	0.45551	0.12503	-0.06198
npentana	-0.39357	0.33126	-0.26557	-0.14075
v2butoxy	0.06924	0.32639	-0.36027	0.56445
v2propa2	0.06923	0.33900	0.27007	0.56396

The four principal components were identified as motor vehicle emissions (mvexhr),

building materials (bldgmr), carpet/building materials (styrenr), and water-based paints

and solvents (v2butoxr). The principal component coefficients ("scoring coefficients") are

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estimated by the analysis for each of the 10 VOCs. That is, principal component analysis

iteratively develops coefficients for each VOC which reflect the association (positive or

negative) of an individual VOC with an identified source. These are presented below.

```
. score mvexhr bldgmr styrenr v2butoxr
            (based on unrotated principal components)
          Scoring Coefficients
 Variable |     1          2          3          4
----------+-----------------------------------------------
  styrene |   0.03026    0.04230    0.81371   -0.01512
 ethylace |  -0.32482    0.45684    0.12451   -0.24997
 butylace |   0.28739    0.09775    0.07875    0.28932
 vl24trim |   0.42350    0.28730    0.06470   -0.22617
 mpxylene |   0.41775    0.27163   -0.10147   -0.28952
  oxylene |   0.42125    0.29145   -0.11313   -0.24146
 nhexanal |  -0.33939    0.45551    0.12503   -0.06198
 npentana |  -0.39357    0.33126   -0.26557   -0.14075
 v2butoxy |   0.06924    0.32639   -0.36027    0.56445
 v2propa2 |   0.06923    0.33900    0.27007    0.56396
```

As described in Appendix D, the principal components are sums of the standardized value

of the ith variable for case k multiplied by the estimated principal component coefficient of

principal score coefficient for the ith variable and the jth principal component, as per the

equation below (Appendix D). That is, the principal components which represent

identified sources are composed of the sum of the original VOC concentration multiplied

by the estimated principal component coefficient for each VOC.

$$Principal\ Component\ = P_k^{(j)} = \left(\sum_{i=1}^{n} a_{ij} X_{ik} \right)$$

This calculation is shown for the principal component identified as the water-based paints

and solvents source (v2butoxr) and the principal component identified as the carpet/

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building materials source (styrenr). These two source vectors comprise the Irritancy/PC

metric. Test variables "test2BE" and "teststy" are presented below.

```
. gen test2BE= styrens* -0.01512+ ethylacs* -0.24997+ butylacs* 0.28932+
v124tris* -0.22617+ mpxylens* -0.28952+ oxylens* -0.24146+ nhexanas* -
0.06198+ npentans* -0.14075+ v2butoxs* 0.56445+ v2propas* 0.56396
. gen teststy=
styrens*0.81371+ethylacs*0.12451+butylacs*0.07875+v124tris*0.0647+mpxyle
ns*-0.10147+oxylens*-0.11313+nhexanas*0.12503+npentans*-
0.26557+v2butoxs*-0.36027+v2propas*0.27007
```

The test variables compare extremely favorably to the principal components calculated by

the computer algorithm.

```
. list spacenum test2BE v2butoxr teststy styrenr
       spacenum      test2BE    v2butoxr      teststy      styrenr
  1.         11     2.198645    2.198638    -1.599244     -1.59924
  2.         12      .2422034    .242208     -.9714772    -.9714794
  3.         21      .6113542    .611358     -.5148904    -.5148926
  4.         22      .2153618    .215368     -.9601534    -.9601548
  5.         33     -.7535568   -.7535488   -1.258822    -1.258824
  6.         41     -.8289035   -.8289232     .8832672     .883271
  7.         42     -.8873934   -.8874158    1.085971     1.085975
  8.         51     -.6380222   -.6380225   -1.049334    -1.049334
  9.         53     -.8708146   -.8708085   -1.349422    -1.349414
 10.         61      .6654224    .6654254   -2.228748    -2.228745
 11.         71     2.738676    2.738665     1.477771     1.47779
 12.         72      .2140675    .214075      .5076631     .5076635
 13.         81     -.4784285   -.4784218    -.1847117    -.1847112
 14.         82     -.4340834   -.434078     -.3178218    -.3178211
 15.         91    -1.378512   -1.378505      .14463       .1446279
 16.         93    -1.546581   -1.546571     -.0820212    -.0820217
 17.         94    -1.11113    -1.111127     1.24939      1.249384
 18.        101      .5076174    .5076175    1.012647     1.012641
 19.        102      .6754709    .6754669    1.018496     1.018489
 20.        103      .6648975    .6648975     .6830295     .6830223
 21.        111     -.1283778   -.1283821    1.574138     1.574136
 22.        121      .3220853    .322085      .8796428     .8796389
```

As described in the text, principal component coefficients are iteratively calculated to

fulfill two requirements: 1) the principal components are linearized sums that retain

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information from the original multivariate measurements; 2) the principal components are

uncorrelated measures. The first condition was met. As seen below, the second condition

was also met, as correlations among four principal components are zero.

```
. correlate mvexhr bldgmr styrenr v2butoxr
(obs=22)
         |    mvexhr    bldgmr   styrenr v2butoxr
---------+---------------------------------------
  mvexhr |    1.0000
  bldgmr |   -0.0000    1.0000
 styrenr |   -0.0000   -0.0000    1.0000
v2butoxr |   -0.0000   -0.0000   -0.0000    1.0000
```

Calculated principal components were linked to the symptom data base by space number.

The final data file used in the logistic regression analyses contains information on 517

subjects located in 22 spaces for which principal components were estimated. The ability

of new VOC exposure metrics to predict SBS symptoms can be tested for both crude

(unadjusted for potential bias) and adjusted (adjusted for potential sources of bias)

analyses. Examples of crude and adjusted ORs of the Irritancy/PC exposure metric for the

skin symptom are presented below.

The Irritancy/PC exposure metric is composed of two source vectors (the water-based

paints and solvents source and the carpet/building materials source). Crude ORs were

calculated using logistic regression. As seen below, the crude OR for the water-based

paints and solvents source (v2butoxr, $p < 0.006$) is highly significant, but the carpet/

building materials source (styrenr, $p > 0.3$) is less significant for this symptom.

```
. logistic skinw3 styrenr v2butoxr
Logit Estimates                      Number of obs =     395
                                     chi2(2)       =    8.09
                                     Prob > chi2   =  0.0175
```

```
Log Likelihood =  -149.8088                    Pseudo R2     = 0.0263
```

skinw3	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
styrenr	1.151328	.1494843	1.085	0.278	.8926523	1.484965
v2butoxr	1.564525	.2567743	2.727	0.006	1.134177	2.158163

```
. lrtest, using(0)
Logistic:  likelihood-ratio test              chi2(18)      =      39.95
                                               Prob > chi2 =      0.0021
```

The results for the crude ORs are reflected in the results for the adjusted ORs. First, the

full model is estimated using all risk factors and covariates.

```
. logistic skinw3 styrenr v2butoxr white agegt39 schlgth smokever gender sensitiv
prof tech clerical jobothr casework ac mv tmp rh copytim pntnew problem
```

```
Logit Estimates                                Number of obs =      395
                                               chi2(20)      =    48.04
                                               Prob > chi2 = 0.0004
Log Likelihood = -129.83522                    Pseudo R2     = 0.1561
```

skinw3	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
styrenr	1.179968	.3117799	0.626	0.531	.7030066	1.980528
v2butoxr	2.160127	.5990508	2.777	0.005	1.25436	3.719943
white	.8032491	.3025005	-0.582	0.561	.3839644	1.680388
agegt39	.3213236	.1684634	-2.165	0.030	.1149939	.8978634
schlgth	1.065981	.4819018	0.141	0.888	.4394845	2.585563
smokever	1.029655	.3508187	0.086	0.932	.52805	2.007746
gender	2.645483	1.120518	2.297	0.022	1.153375	6.06791
sensitiv	1.477705	.502232	1.149	0.251	.7590799	2.876658
prof	1.847536	1.345289	0.843	0.399	.4433918	7.698357
tech	3.455309	2.788681	1.536	0.124	.7104056	16.80611
clerical	1.660689	1.014736	0.830	0.406	.5013906	5.500481
jobothr	3.598399	3.697333	1.246	0.213	.4802916	26.95961
casework	1.040712	.6971618	0.060	0.952	.2799755	3.868488
ac	1.488022	1.125329	0.526	0.599	.3379724	6.551449
mv	2.54974	2.097081	1.138	0.255	.5086387	12.78152
tmp	1.253847	.4480318	0.633	0.527	.6224268	2.52581
rh	.8553936	.091743	-1.456	0.145	.6932224	1.055503
copytim	1.01107	.005635	1.975	0.048	1.000086	1.022175
pntnew	1.619285	.9452971	0.826	0.409	.5157198	5.084321
problem	2.481448	1.801477	1.252	0.211	.5980694	10.29577

```
. lrtest, saving(0)
```

Next, the maximum likelihood is estimated for a model without the Irritancy/PC exposure metric.

```
. logistic skinw3 white agegt39 schlgth smokever gender sensitiv prof tech cler
> ical jobothr casework ac mv tmp rh copytim pntnew problem

Logit Estimates                                  Number of obs =      395
                                                 chi2(18)      =    38.82
                                                 Prob > chi2   = 0.0030
Log Likelihood = -134.44223                      Pseudo R2     = 0.1262

--------------------------------------------------------------------------------
  skinw3 | Odds Ratio   Std. Err.      z     P>|z|     [95% Conf. Interval]
---------+----------------------------------------------------------------------
   white |  .6107805        .216    -1.394   0.163     .3053945    1.221544
 agegt39 |  .4089053    .2013431    -1.816   0.069      .155774    1.073372
  schlgth|  1.163388    .5164066     0.341   0.733      .487407    2.776882
 smokever|  .9715341    .3249898    -0.086   0.931     .5043372    1.871523
  gender |  2.093007    .8545602     1.809   0.070     .9402229    4.659189
 sensitiv|   1.41682    .4709883     1.048   0.295     .7385038    2.718169
    prof |  1.748889     1.24009     0.788   0.431     .4357108    7.019824
    tech |  2.498378    1.917067     1.193   0.233     .5552781    11.24102
 clerical|  1.681242    1.003409     0.870   0.384     .5219284    5.415638
  jobothr|  3.070003    3.044753     1.131   0.258      .439479    21.44566
 casework|  1.241832    .8422962     0.319   0.749     .3286392    4.692524
      ac |  1.512027     1.15658     0.541   0.589     .3376432    6.771128
      mv |  1.145355    .8436484     0.184   0.854     .2703707    4.851994
     tmp |  1.609844     .429693     1.784   0.074      .954079    2.716333
      rh |  .9700754    .0783463    -0.376   0.707     .8280562    1.136452
 copytim |  1.012091    .0054516     2.231   0.026     1.001462    1.022833
  pntnew |   .922388    .4885611    -0.153   0.879     .3266313     2.60477
 problem |  2.675701    1.595028     1.651   0.099     .8318071    8.607014
--------------------------------------------------------------------------------

. lrtest, using(0)
```

The effectiveness of the VOC exposure metrics in prediction of SBS symptoms in an adjusted model was evaluated by chi-square comparisons of maximum likelihood estimations of models with and without the VOC metric. For the skin symptom, this chi-square comparison demonstrates the two models differ significantly when the VOC exposure metric is removed (χ^2=9.2, p < 0.01).

```
Logistic: likelihood-ratio test        chi2(2)     =      9.21
                                        Prob > chi2 =    0.0100
```

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