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Development of New Volatile Organic Compound (VOC Exposure Metrics and their Relationship to "Sick Building Syndrome" Symptoms

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Abstract Occupants of office buildings are exposed to low concentrations of complex mixtures of volatile organic compounds (VOCs) that encompass a number of chemical classes and a broad range of irritancies. "Sick building syndrome" (SBS) is suspected to be related to these exposures. Using data from 22 office areas in 12 California buildings, seven VOC exposure metrics were developed and their ability to predict self-reported SBS irritant symptoms of office workers was tested. The VOC metrics were each evaluated in a multivariate logistic regression analysis model adjusted for other risk factors or confounders. Total VOCs and most of the other metrics were not statistically significant predictors of symptoms in crude or adjusted analyses. Two metrics were developed using principal components (PC) analysis on subsets of the 39 VOCs. The Irritancy/PC metric was the most statistically significant predictor of adjusted irritant symptoms. The irritant potencies of individual compounds, highly correlated nature of indoor VOC mixtures, and probable presence of potent, but unmeasured, VOCs were variously factored into this metric. These results, which for the first time show a link between low level VOC exposures from specific types of indoor sources to SBS symptoms, require confirmation using data sets from other buildings.

Key words Volatile organic compounds (VOC); Sick building syndrome (SBS); Total volatile organic compounds (TVOC); Office buildings; Indoor sources.

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Introduction

There is now a large body of evidence that "sick building syndrome" (SBS) symptoms are widely experienced by office workers in Europe and the Un States. SBS is defined by the World Health Organ tion as a complex of subchronic symptoms that o while occupants are in a building and generally crease when they leave. The symptoms include i tation of the eyes, nose, or throat, headache, fati dry or itchy skin, and difficulty breathing or c tightness. SBS is most evident in the extreme case which the building occupants experience unusually vere, frequent, or widespread symptoms. Survey office buildings conducted in the U.S. and in Eur suggest that 20% or more of occupants in buildi without known problems frequently experience symptoms (Hedge et al., 1989; Norback and Torg 1990; Skov et al., 1990; Mendell, 1991; Zweers et 1992; Mendell et al., 1996).

There are several reasons for suspecting that vola organic compounds (VOCs) are a factor in SBS sym toms. Industrial exposures to VOCs cause the kinds symptoms observed for SBS. However, industr workers are typically exposed to only one or a f VOCs at very high concentrations. In office buildin workers are typically exposed to perhaps a hundr or more VOCs, each at a concentration that is abou hundred- to a thousand-fold lower than the conc trations known to cause such symptoms. For this r son, it has been suggested that the *total* concentrati of all VOCs (TVOC) is a causative factor in SBS sym toms. Concentrations of TVOC in office buildings typically about 0.5 mg/m^3, although in some buildin TVOC reaches levels of 2–10 mg/m^3. Studies in

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vironmental chambers with simple mixtures of VOCs at high total concentrations (5–25 mg/m^3) suggest that exposures to high concentrations can induce SBS symptoms (Molhave et al., 1986; Kjaergaard et al., 1989). Studies in buildings have not generally been able to find relations between measured VOCs and SBS symptoms, except at high concentrations. However, SBS symptoms are reported even for buildings with low TVOC concentrations. There have been just a few studies in which relationships between low-level VOC exposures and SBS symptoms were reported. Norback and Torgen (1990) reported associations between TVOC and airway (nasal), general and eye symptoms at total hydrocarbon levels of 130 μg m^{-3}; however, TVOC measurements were made 6 months to 4 years after questionnaire data were gathered. Hodgson et al. (1991) reported associations between VOC concentrations and central nervous symptoms, but the relationship was weak when compared with associations between work stress and complaints. Sundell et al. (1993) reported negative correlations between TVOC concentrations and symptom prevalences for 29 office buildings in northern Sweden with low TVOC concentrations. They also found that the TVOC concentrations were generally lower in the room air than in the supply or intake air. The authors suggested that these results might be related to chemical reactions of some of the TVOCs to form more irritating VOCs, such as formaldehyde.

In the work reported here, it was hypothesized that there is an association between reported SBS symptoms and exposures to VOCs at low concentrations but that better exposure metrics than TVOC are needed. The term "exposure metric" refers to the measurement and mathematical expression of the potential or actual agent (or combination of agents) that causes an adverse health effect.

In this study, a number of different exposure metrics were developed and tested for the mixtures of VOCs commonly found in indoor air using data collected in the California Healthy Buildings Study (Fisk et al., 1993). In developing exposure metrics for VOCs, it was hypothesized that the variability of the biological potencies of VOCs should be taken into account. Because some of the VOCs are highly correlated due to common sources, the study also considered how to reduce the number of VOCs to a smaller number of factors that could be related to sources. The study focused on the SBS symptoms of irritancy which involve stimulation of the trigeminal nervous system. For this purpose, a relative irritancy scale for the VOCs was first developed. Multivariate logistic regression analysis was then used to assess the correlation relationships between work-related symptoms and various metrics of VOC exposure while controlling for other factors known to affect symptom reporting.

Approach

Study Description

As part of Phase 1 of the California Healthy Building Study (CHBS) (Daisey et al., 1990; Mendell, 1991; Fisk et al., 1993; Mendell et al., 1996), concentrations of TVOC and of 39 individual VOCs were measured in 12 office buildings in the San Francisco Bay Area in northern California. Self-administered questionnaires (Mendell, 1991) were returned by participants (n=880, 85% response rate) with information on personal, psychological, job and workspace factors, as well as SBS symptoms.

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, none of which were included in this study. The selection criteria were: 1) more than 900 square meters of currently occupied office space; 2) at least 45 full-time and at least 10 clerical workers; 3) no unusual pollutant sources; 4) no ongoing renovations; and 5) one of three ventilation types: naturally ventilated (NV), mechanically ventilated with operable windows and no air conditioning (MV), and mechanically ventilated with sealed windows and air conditioning (AC). Ten of the buildings were located in a moderate climate zone and two of the AC buildings were located in a hot climate zone.[1] One of the AC buildings in the moderate climate was a classic problem building with a long history of occupant complaints, causes of which had never been clearly identified. 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 office spaces with cubicles were chosen where possible; in some cases adjoining offices were included. The buildings were studied between June and September, 1990.

Self-administered questionnaires were used to collect information on the frequency of 15 health symptoms during the previous week and the previous year,

[1] The climate in the San Francisco Bay area varies substantially over relatively short distances. During the summer, the average daily maximum temperature varies from 69°F in San Francisco to 86°F in Contra Costa county to the east. There is essentially no summer rain and generally moderate (<60%) relative humidity.

and on demographic, psycho-social, and job-related parameters (Daisey et al., 1990; Mendell et al., 1996) in the week after the VOC measurements were made. For this investigation of VOC metrics, symptoms reported for the previous week were used.

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-h 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 data for the current investigation of the relationships between occupant symptoms and various metrics of exposure to VOCs are a subset of those from the original survey. Since 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.

Development of Exposure Metrics

In order to take the VOC irritant potencies differences into account, a relative irritancy scale for the VOCs was first developed. As there is limited irritancy data for controlled human exposures to VOCs, the irritancy scale was based on the mouse bioassay developed by Alarie (1966). The mouse bioassay determines the RD_{50}, the concentration of airborne irritant, which causes a 50% decrease in the breathing rate in exposed mice. The bioassay has been used to test many individual VOCs and the results are highly correlated with thresholds set to protect humans (Alarie, 1981). Missing data for some VOCs was estimated from correlations between the RD_{50} values of the bioassay and vapor pressures, by chemical class (Ten Brinke, 1995). Since relative irritancy was of interest, the RD_{50} of each VOC of interest was referenced to the RD_{50} for toluene. The relative irritancy of the most irritating VOCs is presented in Table 1. There is more than a factor of 100 difference between the most and least irritating VOC in this table.

The exposure metrics which were investigated are summarized in Table 2. These included TVOC; ΣVOC, the sum of the VOCs individually quantified by gas chromatography-mass spectrometry (GC-MS); $\Sigma(Ir_i{*}VOC_i)$, the sum of the VOCs with each weighted by its relative irritancy; $\Sigma(Or_i{*}VOC_i)$, the sum of the VOCs with each weighted by its odor threshold (Devos et al., 1990) relative to toluene; the Chemical Class metric; and two metrics derived using principal compor (PC) analysis of the measured VOCs. For the Chem Class metric, concentrations of VOCs within each five chemical classes were summed and regression efficients were fit for each class in the metric as par the multivariate logistic regression model used to late SBS symptoms and the metrics (described belo

Principal component analysis, which converts hig correlated variables to a reduced number of lineari sums of the individual VOCs, or principal compone (PC), was used to develop two metrics. Correla VOCs tend to group on a single PC because cert groups of VOCs increase or decrease in concentrat together because they have a common source ty Some VOCs originate from more than a single sou type and are then associated with more than one l Thus, this methodology can apportion the VOC amo its sources. The PCs may also trace the presence other compounds that are probably present but are sampled and analyzed with the usual VOC method

The PC metrics were obtained by principal com nent analysis of different subsets of the 39 VOCs. principle, all available VOCs could be used in the pr cipal component analysis. For the CHBS data set, ho ever, there were only 22 cases (sites) for which a co plete set of VOC measurements and SBS sympto were available. To obtain more robust PC solutio smaller subsets of 10 or 11 out of the 39 VOCs w used in the analysis (Henry et al., 1984). The subs

Table 1 Ordered relative irritancy scale for 22 VOCs measured the California Healthy Buildings Study

Compound	Chemical Class	Relative Irritanc Referenced to Toluene
Styrene	Aromatic	7.9
Ethylacetate	Ester	7.6
n-Butyl acetate	Ester	6.2
1,2,3-Trimethylbenzene	Aromatic	4.1
n-Hexanal	Aldehyde	4.0
n-Pentanal	Aldehyde	3.9
1,2,4-Trimethylbenzene	Aromatic	3.6
m/p-Xylene	Aromatic	3.4
1,3,5-Trimethylbenzene	Aromatic	3.16
2-Ethyltoluene	Aromatic	3.15
o-Xylene	Aromatic	3.08
3/4-Ethyltoluene	Aromatic	2.9
Ethylbenzene	Aromatic	1.7
2-Butoxyethanol	Alcohol	1.6
Toluene	Aromatic	1 (reference)
Benzene	Aromatic	0.46
2-Propanol	Aromatic	0.40
n-Heptane	Alkane	0.26
n-Octane	Alkane	0.25
Ethanol	Alcohol	0.17
2-Propanone (acetone)	Ketone	0.09
n-Nonane	Alkane	0.07

Table 2 VOC exposure metrics

Metric symbol	Description	Exposure metric as used in regression equation[a]
TVOC	Mass sum of VOCs measured with flame ionization detector	$\beta_T \cdot$ TVOC
ΣVOC_i	Sum of individual VOCs quantified by GC/MS	$\beta_S \cdot \Sigma(VOC)_i$
$\Sigma(Ir^*VOC)_i$	Sum of irritancy-weighted individual compounds. Irritancy weighting based on irritancy relative to toluene (Table 1)	$\beta_I^* \Sigma(Ir_i *VOC_i)$ *where* Ir_i*=relative irritancy weighting factor for* VOC_i
$\Sigma(Or^*VOC)_i$	Sum of odor-weighted individual compounds. Odor weighting based on odor relative to toluene[b]	$\beta_O^* \Sigma(Or_i *VOC_i)$ *where* Or_i*=relative odor weighting factor for* VOC_i
Chemical class	Concentrations of individual compounds summed into five chemical classes: Aromatics, Alkanes, Terpenes, Chlorinated, and Oxidized Hydrocarbons	β_i (Aromatic)+β_j (Alkane)+β_k(Terpene)+β_l(Chlorinated)+β_m(Oxidized) *where: (Chemical Class)=Sum of concentrations of the VOCs in each class, and* β_i, β_j, β_k, β_l, *and* β_m *are multiple regression coefficients from logistic regression analyses*
AF/CP source vector	VOCs preselected based on prior source identification and source strengths, using the I/O ratio; principal component vector 4, $P_S(4)$, produced by PCA[c] and identified as due to Air Fresheners and Cleaning Products is used as exposure metric	β_{S4} $P_s(4)$
Irritancy/PC	VOCs preselected based on relative irritancy scale and prior source identification; sum of two of the principal components produced by PCA, P(3) & P(4), used as exposure metric	β_3 P(3)+β_4 P(4)

[a] β's are regression coefficients from the logistical regression equations
[b] Odor thresholds, taken from Devos et al. (1990), were ordered relative to toluene using the same method as described for irritancy; however, the results are not shown. The CHBS VOCs were well below odor thresholds, i.e., no odor(s) dominated. As an odor threshold ordered scale may not be valid due to low exposure levels and the non-additivity of odor thresholds, the ordered scale was not reported; however, it was used in an exploratory manner
[c] Principle components analysis

were selected on the basis of potential sources and source strength and relative irritancy of the VOCs.

An important underlying assumption of the current analysis is that each VOC exposure metric provides some measure of the irritant potency of VOC mixtures. This assumption is weakest for TVOC and the ΣVOC_i variants. A reasonable hypothesis is that an irritant- or odor-weighted sum of VOCs might be useful in a model of sensory irritant symptom prediction. The chemical class metric is intermediate between the TVOC and irritant-weighted metrics. The principal component analysis is based on the assumption that emissions from different types of sources have different relative irritancies, and that there could be direct relationships to SBS irritant symptoms. The results of the analysis will indicate that this hypothesis has some merit, provided that the appropriate irritant VOCs are included in the analysis, as seen in the predictive power of the Irritancy/PC metric.

In the principle components analysis, the initial emphasis was on identifying VOC sources that were common across the buildings and VOCs were selected for inclusion in the analysis using a criterion of potential source strength, as described previously (Daisey et al., 1994; Ten Brinke, 1995). That is, the VOCs with the highest or lowest indoor/outdoor (I/O) concentration ratios in eight or more of the 12 study buildings were selected. VOCs with high I/O ratios, predominantly indoor sources, and their tentatively identified sources included dichloromethane, trichloroethylene, 1,1,1-trichloroethane (cleaning and degreasing products); ethanol, 2-propanol, 2-propanone (bioeffluents and building materials); n-dodecane, n-pentanal, n-hexanal, limonene (air fresheners, building materials and cleaning products). Conversely, VOCs with low I/O ratios have strong outdoor sources; these included: benzene, m&p-xylene, o-xylene, 2-ethyltoluene, 3&4-ethyltoluene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, n-pentane, 3-methylhexane (motor vehicle emissions); tetrachloroethylene (dry cleaning); n-decane and n-nonane (Other). A subset of 11 VOCs was selected that included compounds from all of the tentatively identified sources: trichloroethylene, ethanol, n-dodecane, n-hexanal, limonene, benzene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, tetrachloroethylene, n-decane, and n-nonane.

Four vectors were obtained from the PC analysis of VOCs selected based on source strengths. These were identified as: $P_S(1)$, motor vehicle emissions; $P_S(2)$, dry cleaning emissions; $P_S(3)$, bioeffluents and building materials; and $P_S(4)$, room air fresheners/deodorizers and cleaning products, where the "S" subscript indicates that the VOCs were selected based on source strengths. Only the sources represented by the fourth principal component were found to be useful in symptom prediction, and for brevity, only this metric, designated the AF/CP Source Vector, is presented and discussed here. The most highly loaded VOC on this vector was limonene, which is used widely in cleaning products (Lebret et al., 1986; Wallace, 1986), followed by n-decane and n-nonane, which are major components of air fresheners and deoderizers (Tichenor, 1989; Levin, 1989).

For the Irritancy/PC metric, a different subset of 10 VOCs were selected for PC analysis based on relative irritancy (Table 1) and on the four sources of the VOCs identified in previous analyses. For example, five of the 10 most irritating VOCs were from the group of VOCs previously identified as coming from motor vehicle emissions. In order to allow inclusion of VOCs from other sources, only three of the five were included, i.e., 1,2,4-trimethylbenzene, m&p-xylene and o-xylene. Table 3 presents the loadings of the selected VOCs on each of the principal components of the Irritancy/PC exposure metric. The loadings are correlations of the VOCs with the PC vectors. The greater the value of the loading, the greater the correlation with a given PC. The source identifications of the vectors were based on the most highly correlated VOCs for each of the vectors, indoor-outdoor concentration ratios, and information from the literature on the sources of the these VOCs (Berglund et al., 1989; Clausen et al., 1990; Daisey et al., 1994; Hodgson and Wooley, 1991; Hodgson et al., 1993; Lebret et al., 1986; Levin, 1989; Plehn, 1990; Sheldon and Pellizzari, 1994; Wallace, 1986; Wallace et al., 1987; Wallace, 1989; W off et al., 1993).

Irritant Symptom Prevalences

Work-related irritant symptom prevalences from questionnaire data were used as dependent variable multiple logistic regression analyses. These are su marized in Table 4. A symptom was considered w related if it was reported as being experienced wi the office building, but improving on days not in the fice. Binary symptom outcomes (yes/no) were base whether individuals experienced a work-related sy tom three or more days in the last week, with q tionnaire administration timed so that "last week" the week of VOC sampling. Specific work-related sy toms were obtained from individual symptom q tions: dry, irritated or itching eyes (eye); dry or itchy (skin); dry or irritated throat (throat); chest tight (chest); difficulty breathing; runny nose; stuffy n sleepiness; fatigue; headache. Subjects were also q ied regarding three symptoms believed not to be pa the SBS syndrome (earache, shoulder pain or numb toothache), in order to estimate symptom ove porting. However, prevalences of earache and tooth were generally too low for analysis. Only shoulder or numbness was retained. Three composite symp variables were developed based on at least one pos report of any of the specified individual work-rel symptoms. The irritant symptom variable was c posed of eye, skin, or throat symptoms. The irrit mucus membrane variable was composed of eye, th runny nose, or stuffy nose symptoms. The overall able was composed of general systemic symptoms (chest, difficulty breathing, runny nose, stuffy n sleepiness, fatigue, or headache).

Table 3 Results of principal component analysis on VOCs selected for irritancy and sources

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
Hexanal	−0.34	0.46	0.13	−0.062	0.89
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 Identity:	Motor vehicle emissions	Building materials	Carpets and building materials	Cleaning products & waterbased paint	

Table 4 Definitions of symptoms (individual and composite) used as dependent variables

Symptom Abbreviations	Symptoms
Individual symptoms:	
Eye	Dry, irritated, or itching eyes
Skin	Dry or itchy skin
Throat	Dry or irritated throat
Chest tightness	Chest tightness
Difficulty breathing	Difficulty breathing
Runny nose	Runny nose
Stuffy nose	Stuffy nose
Sleepiness	Sleepiness
Fatigue	Fatigue
Headache	Headache
Shoulder	Shoulder pain or numbness
Composite symptoms:	
Irritant	Reporting at least one of the following: eyes, skin, throat
Irritated mocous membrane	Reporting at least one of the following: eyes, runny nose, stuffy nose, throat
Overall	Reporting at least one of the following: chest, difficulty breathing, runny nose, stuffy nose, sleep, fatigue, headache

Logistic Regression Analytic Methods

Multivariate logistic regressions (Stata version 3.1) were used to assess the relationships between work-related symptoms and various metrics of VOC exposure. The odds ratio (OR) was 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 and adjusted ORs were estimated for 10 individual work-related (dependent) variables, one non-SBS symptom variable, and three composite variables. Chi-square comparisons of models with and without VOC exposure metrics were used to evaluate the influence of each of the seven exposure metrics on individual and composite symptoms. Additionally, regression coefficients per unit increase of the independent variable were used to assess the importance of the independent variables.

Additional variables were included in the full model based on their ability to confound or obscure relationships between VOC exposures and SBS symptoms (Table 5). Categorical independent variables were represented by dichotomous indicator variables for each level; the reference levels were not included in the model. The final models contained all terms for demographic variables, potential indicators of source of exposures to VOCs, ventilation type, temperature, relative humidity, and sensitive subpopulations (asthmatics, individuals with allergies, ever smokers, problem building status). VOC metrics were tested in models adjusted for these factors.

Table 5 Other independent variables included in the logistic regression models

Other Independent Variables, Grouped by Type
Gender, age, race, education, job classification
Time using copy machine, new paint nearby
Ventilation type
Temperature, relative humidity
Asthmatics, individuals with allergies, ever smokers, problem building status

Results

Most of the tested metrics shown in Table 2 were not effective in predicting the SBS irritancy symptoms in the logistic regression model, including the most common VOC exposure metric, TVOC. The VOC metric that took into account irritant potency, but did not adjust for the highly correlated nature of the data set or for the presence of VOCs that were not measured, was also not a statistically significant predictor of irritant symptoms. The AF/CP Source Vector metric was useful in a model with data from all available buildings, which included spaces where TVOC levels were 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 (the symptom that represented over-reporting). Logistic regression estimates of the impact of earache and toothache would not converge, due to the low number of symptoms reported.

Crude ORs (not shown) for the AF/CP Source Vector metric, which were based only on the cleaning products source vector from the sources PC analysis, were low ($1.3\geq$ OR ≤ 1.5) but significant (CIs excluded 1.0) for all but the chest symptom. However, adjusted ORs for the AF/CP Source Vector metric were not stat-

Table 6 Irritancy/PC and AF/CP source vector metrics in an adjusted model: Chi-square comparisons of maximum log-likelil estimations, with and without metrics

Symptom	Irritancy/PC			AF/CP source vector		
	χ^2	P<	N	χ^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 Mocous Membrane	14	0.001	419	5.1	0.02	419
Shoulder	3.1	0.21	392	0.3	0.55	392

Table 7 Crude and adjusted ORs for statistically significant vectors of the irritancy metric

Symptom	Cleaning products & water-based paints vector, P(4)				Carpet/building materials vector, P(			
	Crude		Adjusted		Crude		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95%
Eye	1.3	1.0–1.7	1.7	1.1–2.7	1.2	1.0–1.5	1.6	1.1–2
Skin	1.6	1.1–2.2	2.2	1.3–3.7	1.2	0.9–1.5	1.2	0.7–2
Throat	1.3	1.0–1.8	1.8	1.1–3.1	0.9	0.7–1.1	0.9	0.6–1
Irritant	1.3	1.0–1.6	1.8	1.2–2.7	1.1	0.9–1.3	1.4	1.0–1
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
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
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
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
Sleepiness	1.6	1.2–2.1	1.6	1.0–2.4	1.1	0.9–1.4	1.5	1.0–2
Fatigue	1.2	0.9–1.5	1.3	0.9–2.0	1.0	0.8–1.2	1.1	0.8–1
Headache	1.4	1.0–2.0	1.4	0.8–2.3	1.1	0.8–1.4	1.2	0.8–1
Overall	1.7	13–2.2	1.8	1.2–2.7	1.1	0.9–1.3	1.1	0.8–1
Irritated mucous membrane	1.4	1.1–1.7	1.8	1.2–2.7	1.1	0.9–1.3	1.4	1.0–1
Shoulder	1.1	0.8–1.6	1.7	0.9–3.2	1.0	0.7–1.3	0.9	0.6–1

istically significant, except for the stuffy nose (OR=1.6), sleepiness (OR=1.4) and the composite irritated mucous membrane (OR=1.4) symptoms.

In contrast, the Irritancy/PC exposure metric was an effective and statistically significant predictor of several SBS irritant symptoms, including skin irritation. Initially, all four vectors were tested against irritant symptoms. The carpet/building materials and cleaning products & water-based paints emissions vectors (Table 3) were found to be more influential than the other the two principal components in symptom prediction, i.e., the sources represented by the first (motor vehicle emissions) and second principal component (building materials emissions) were not irritating as measured by their ability to be useful in symptom prediction. Thus, the Irritancy/PC exposure metric was defined as the sum of principal components three and four.

Table 6 presents the results of Chi-square comparisons for the Irritancy/PC and AF/CP Source Vec metrics in an adjusted model. Symptoms for which Irritancy/PC metrics showed significant correlati (P<0.05) included: eye, skin, irritant, stuffy n sleepiness, overall, and irritated mucous membrane contrast, the AF/CP Source Vector metric was sign cant for only two symptoms, stuffy nose and irrita mucous membrane (P<0.05).

The Irritancy/PC exposure metric was composed the two principal components representing the m irritating VOCs emitted from carpets and building n terials, and from cleaning products and water-bas paints, P(3) and P(4), respectively, in Table 3. Tabl compares the crude and adjusted ORs and 95% co dence intervals (95% CI) for the two separate vect P(3) and P(4), of the Irritancy/PC metric. Crude C for the cleaning products and water-based pai source vector, P(4), were statistically significant for irritant variables, but not for headache, fatigue and the non-SBS symptoms (shoulder pain and numbness). Crude ORs for the carpet/building materials source vector, P(3), were near 1.0 and were not statistically significant (95% CIs did not include 1.0).

Adjusted ORs for P(4) are also presented in Table 7. In general, the adjusted ORs were slightly larger than crude ORs. Elevated and statistically significant (95% CIs excluded 1.0) ORs were calculated for the following symptoms: 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. Adjusted ORs for the carpet/building materials source were less significant; after adjustment, only the eye, irritant, sleepiness, and irritated mucous membrane symptoms had elevated statistically significant ORs. Thus, of these two vectors, P(4) was more important in symptom prediction.

Discussion

In this study, a number of new metrics of VOC exposure were developed and tested with respect to their ability to predict self-reported SBS irritancy symptoms. Chi-square comparisons of models with and without VOC exposure metrics were used to evaluate the influence of seven different exposure metrics on individual and composite symptoms. Only two of the seven exposure metrics, the Irritancy/PC and the AF/CP Source Vector metrics, were statistically significant in models of symptom prediction (Table 6). The Irritancy/PC metric had more statistically significant predictive power than the AF/CP Source Vector metric. The Chi-square comparison of the maximum likelihood estimations with and without the Irritancy/PC metric were most statistically significant for the eye, skin and the two composite irritant symptoms. For example, χ^2 was 12 (P<0.003) for the eye irritation symptom. For the AF/CP Source Vector exposure metric, only the symptoms of stuffy nose and the composite irritated mucous membrane symptoms were statistically significant.

The Irritancy/PC Exposure Metric

Although both vectors of the Irritancy/PC metric have predictive power for the irritant symptoms, the adjusted ORs for the individual vectors indicated that the cleaning products & water-based paints source vector, P(4), accounts for a significant proportion of the observed association of irritant symptoms with this metric (Table 7). Adjusted ORs for the P(4) vector were substantially elevated and statistically significant: 1.7 (95% CI 1.1–2.7), 2.2 (95% CI 1.3–3.7), 1.8 (95% CI 1.2–2.7) and 1.8 (95% CI 1.2–2.7) for eye, skin, irritant, and irritated mucous membrane symptoms, respectively. Adjusted ORs for the carpet/building materials vector, P(3), were somewhat lower but statistically significant for the eye, irritant and irritated mucous membrane, and sleepiness symptoms.

The association of the adjusted Irritancy/PC metric with skin symptoms was noteworthy. The large and statistically significant chi-square change in the model of skin irritation due to removal of the Irritancy/PC metric (OR=9.2, P<0.01, see Table 6) is likely to be dominated by the cleaning products & water-based paints source vector (OR=2.2, 95% CI 1.3–3.7), since the adjusted OR for the carpet/building materials source vector, P(3), was small and non-significant (OR=1.2, 95% CI 0.7–2.0).

The P(4) vector was identified as being related to emissions from cleaning products & water-based paints. Many cleaning products used in buildings contain 2-butoxyethanol and a metabolite of this compound has been found in urine samples collected from building cleaners (Vincent et al., 1990). Irritant symptoms (eye, nose and throat) and headaches due to occupational exposures of water-based paints and cleaning products containing 2-butoxyethanol and other glycol ethers have been reported in a comprehensive review of toxicological studies (Hansen et al., 1987). Water-based paints contain both glycol ethers, such as 2-butoxyethanol, as well as 2-propanol (Hodgson and Wooley, 1991; Sheldon and Pellizzari, 1994). Thus, the relationships observed here between the cleaning products & water-based paints PC exposure metric and the prevalences of irritant symptoms in office workers seem reasonable.

In addition to finding eye and skin irritation from occupational exposures to water-based paints containing glycol ethers, Wieslander et al. (1994) found that the number of years of exposure to water-based paints was related to a decrease in forced expiratory volume. In the CHBS, the P(4) vector gave a relatively high adjusted OR for chest tightness (OR=1.8), although the relationship did not reach statistical significance (CI 95% 0.8–4.0).

Johanson and Boman (1991) reported that dermal uptake of 2-butoxyethanol accounted for 75% (45–85%) of the total uptake during whole body exposure to 2-butoxyethanol vapor in a chamber experiment. The dermal exposure route is also important for other glycol ethers and acetates present in cleaning products & water-based paints (Hansen et al., 1987). The dermal uptake reported for painters and cleaners and subjects exposed in environmental chambers are consistent with the findings of an association between skin irritation symptoms and the P(4) vector in the California office workers, although exposures of the office workers to 2-butoxyethanol and related emissions from cleaning products & water-based paints were probably considerably lower than the exposures of the painters and cleaners.

The concentration of 2-butoxyethanol, the most highly "loaded" VOC in the P(4) vector, was also investigated as an exposure metric and found that, although useful for predicting the throat symptom (χ^2= 4, P<0.03; OR=1.1, 95% CI 1.0–1.2), 2-butoxyethanol alone was not a statistically significant predictor of any of the symptoms of irritancy. This suggests that other VOCs associated with emissions from cleaning products & water-based paints and traced by the P(4) vector are an important determinant of the irritant symptoms.

To investigate the potential influence of various building sites on the relationships between the irritation symptoms and the Irritancy/PC metric, the crude prevalences of eye and skin irritation symptoms were plotted versus the values of the P(4) vector at each building and site location. As shown in Figures 1 and 2, the crude prevalences of these two symptoms versus the P(4) vector are suggestive of increased prevalences with increased values of this vector. Both plots show high levels of the cleaning products & water-based paints vector in sites 11 and 71. A total of 29 individuals were located in spaces 11 (n=11) and 71 (n=18). The chi-square comparison between full and nested models with all sites (N=395) was 9.2 (P<0.01).

For the skin irritancy symptom, upon removal of the individuals located in two sites with high vectors (n= 29), the chi-square comparison was 2.8 (P<0.24). This indicates that the elevated values for the cleaning products & water-based paints vector found in spaces 11 and 71 strongly influenced the observed relations between the skin irritant symptom and the Irritan PC metric. Thus, the VOCs traced by the Irritancy/ metric may be actually associated with the prevale of skin symptom, or the symptoms may have b caused by some confounding factor. Since the ove prevalence of skin symptom was relatively l (13.4%), these findings suggest little over-reporting the skin symptom.

Influence of High TVOC Concentrations

There is some evidence from these analyses that VC from liquid-process photocopiers contribute to syn toms of mucosal irritation. Elevated TVOC conc trations were measured in two buildings with liq process photocopiers. TVOC levels in these buildi were 2 to 7 mg m^{-3}, compared to a median value 0.5 mg m^{-3} measured in the other buildings, wh these high TVOC values were excluded. Fifty-sev subjects were located at these locations; 42 and 15 in viduals were located in building 4 (sites 41, 42) a building 5 (site 53), respectively.

The gas chromatograms of the air samples fr these sites were dominated by a mixture of C_{10}–C_{11} i paraffinic hydrocarbons characteristic of emissi from these photocopiers. In chamber experiments w 63 healthy subjects exposed to n-decane (C_{10}), sign cant decreases in tear film stability were observed w exposures of 6 to 20 mg m^{-3} over 6 hours (Kjaergaa et al., 1989). High TVOC concentrations found in t CHBS approached and overlapped with the conce trations observed to cause eye irritation in the chamb study, although the alkanes were not identical.

The influence of high TVOC concentrations on t Irritancy/PC and AF/CP Source Vector metrics w evaluated by removing individuals with high TV

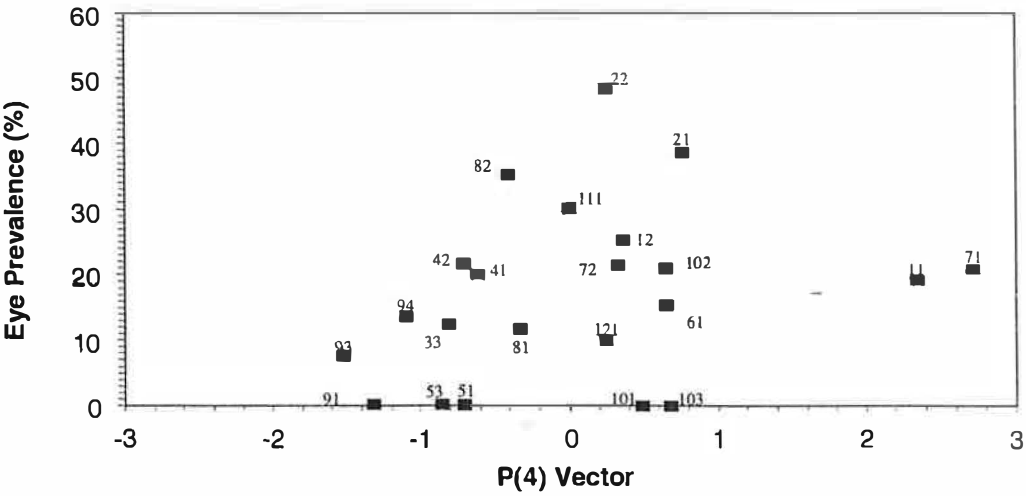

Fig 1 Prevalence of eye sym tom (%) versus value of vec P(4), for cleaning products water-based paints, at ea site. Building and site lo tions are indicated

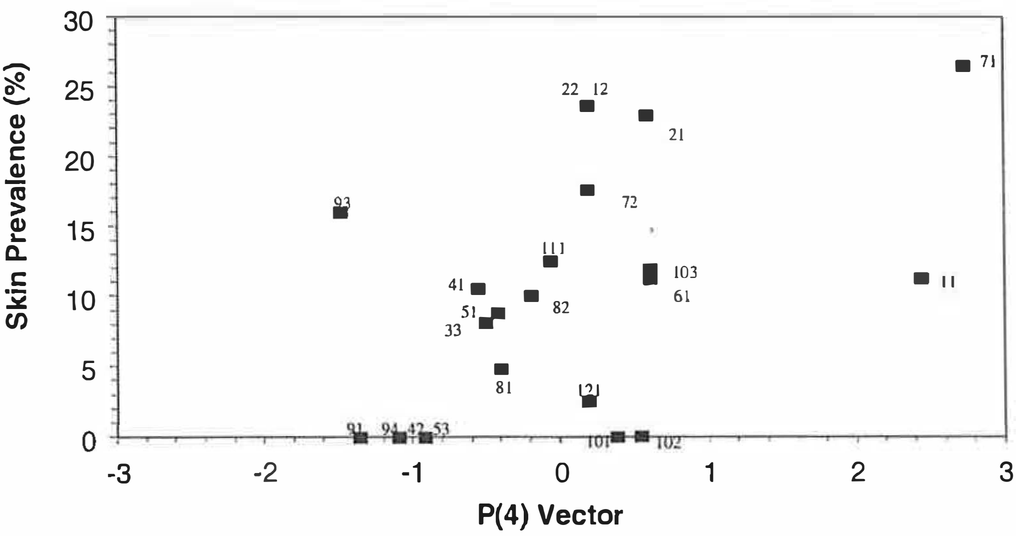

Fig. 2 Prevalence of skin symptom (%) versus value of vector P(4), for cleaning products & water-based paints, at each site. Building and site locations are indicated

exposures. Even with high TVOC exposures excluded, the Irritancy/PC metric was statistically significant in the prediction of irritancy symptoms. Relative to an analysis with all cases, exclusion of these 57 observations at high TVOC sites (11% of the cases) slightly decreased but did not eliminate the predictive ability of the adjusted Irritancy/PC metric. For example, with data from all buildings, significance values were $P<0.003$, $P<0.002$, $P<0.004$ for eye, irritant, and irritated mucous membrane symptoms, respectively. After excluding the high TVOC exposures, the corresponding symptoms remained significant at $P<0.03$, $P<0.01$, and $P<0.001$. By comparison, the ability of the AF/CP Source Vector metric to predict SBS symptoms decreased (e.g., the P-value for the stuffy nose symptom was $P<0.01$ with all data, compared to $P<0.07$ with data from the high TVOC spaces excluded).

Limitations of the Study

There are several limitations to this study that must be noted. First, the VOC sample size in this study was relatively small (22 sites in 12 buildings). Due to limited numbers and spacing of VOC measurement sites, exposures could have been misclassified. Exposure assessment using personal VOC monitors could allow for better assessment of the relationship between VOC exposure and symptom occurrence. Additionally, although the symptom database included 517 individuals, there were a small number of sites with elevated risk factors. For example, 29 individuals were located in 2 sites (11, 71) where the cleaning products & water-based paints vector was elevated. Similarly, 57 individuals were located in 3 sites (41, 42, 53) with high TVOC concentrations. Observed associations may have been due to confounding of other, unmeasured parameters. Further, these results are from a single study and require further investigation and confirmation in other sets of buildings.

Due to the limited number of cases, subsets of VOCs had to be selected for analysis and development of VOC exposure metrics. The selection criteria used here emphasized source strength and irritancy and thus limited the number of source types that could be examined. With a larger data set and fewer restrictions on the VOCs to include in the PC analysis, it should be possible to identify additional sources of VOCs that contribute to SBS symptoms.

Two potentially important sensory irritants, ozone and formaldehyde, were not measured in the CHBS. Ozone is a strong irritant, and is one of the six pollutants for which there are National Ambient Air Quality Standards (NAAQSs). During the period of sampling for the California buildings, the ambient ozone values were very low (0.014–0.048 ppm; Bay Area Air Quality Management District, 1994), although potential indoor sources of ozone, such as photocopiers, were known to be present in the CHBS buildings.

Formaldehyde is commonly found indoors, and the irritant effects of the compound have been well documented; eye and respiratory tract irritation generally occur at levels of about 0.12 mg m^{-3} (0.1 ppm) (World Health Organization, 1989). An attempt was made to sample formaldehyde in the CHBS buildings; however, problems occurred with the sampling system and the measurements were judged unreliable. Polluted urban air concentrations of formaldehyde are typically an order of magnitude below the concentrations known to cause irritant symptoms (Seinfeld, 1986). However, indoor levels of formaldehyde may have been elevated enough to cause or contribute to irritant eye and skin symptoms, although reported measurements for non-problem office buildings are generally quite low (Turk et al., 1987).

The 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.

Exposures to airborne fungi and bacteria were not included in this analysis, although there is evidence that these agents may contribute to SBS symptoms. Measurements of bacteria and fungi were made about one month after all of the other measurements were made in these buildings (Fisk et al., 1993). Concentrations of bacteria and fungi at that time were all below the concentrations that have been suggested as levels of concern (Morey, 1984; Rao et al. 1996). However, the sampling methods for these bioaerosols are limited to about 15 min and thus, do not provide a reliable estimate of workday exposures.

"Sick Building Syndrome" is generally believed to be a multifactorial problem that includes various chemical, physical, psychological and biological factors. The analyses presented here adjusted for many potential confounding factors (e.g., gender, race, job, new paint nearby, ventilation type, temperature, relative humidity, sensitive subpopulations, ever smokers, problem building status). However, other potential sources of bias were not included in the model as they were found to be insignificant (building age). Several other factors could not be included due to measurement limitations. For example, too few cases were reported for "time using carbonless copy paper".

There have been some earlier studies that suggested that SBS symptoms might be related to mechanical ventilation systems, either in etiology (Molhave and Thorsen, 1991) or via the transport of VOCs throughout buildings. In an earlier analysis, Mendell et al. (1996) found elevated symptom prevalence in the CHBS buildings with mechanical ventilation systems, relative to the buildings with natural ventilation. Both this earlier study and the current analysis found no statistically significant associations between TVOC and symptom prevalence; however, as has been discus above, the TVOC metric does not take into account ferences in the irritant effects of different VOC n tures. After adjusting for ventilation type in the curr study, the Irritancy/PC exposure metric and its t vectors were found to be significantly associated w symptoms of irritancy.

The CHBS buildings were chosen to be represe tive of typical office buildings; however, selection quirements may have excluded potential sources VOCs. For example, buildings were excluded if tl contained unusual pollutant sources (e.g., bookbi ing, lacquering). Buildings with on-going renovati were excluded and a non-smoking policy is in ef for all CHBS buildings. Unusual pollutant sour renovations, and/or smoking are all potential sou of VOCs. For example, renovations have been found be almost continual in office buildings, with appro mately 30% of an average office building's inte space completely rebuilt each year (Brooks and Da 1992). Therefore, it is possible that selection criteria cluding buildings with potential sources of VOCs n have biased the results downwards. Further study include a wider range of buildings may find stron relationships between symptoms and VOC expos metrics.

Conclusions

In this study, seven VOC exposure metrics were inv tigated with respect to their ability to predict s reported SBS irritant symptoms in office workers. M were not statistically significant predictors in logisti regressions models. The Irritancy/PC exposure met which took into account the irritancy of the VOCs a their intercorrelations, was a statistically signific predictor of irritant symptoms. The results obtained this study also indicated that emissions from cleani products & water-based paints could account for so of the SBS symptoms observed in office workers in California Healthy Buildings Study.

The most commonly used VOC exposure met TVOC, was not a statistically significant predictor SBS symptoms. In general, TVOC levels were low the CHBS buildings. However, high TVOC conc trations, due to the presence of liquid-process pho copiers (2 to 7 mg m^{-3}), were observed for three si and were within the range of TVOC levels reported cause symptoms in chamber experiments. The analy demonstrated that high TVOC levels at some sites fluenced both the Irritancy/PC and AF/CP Sou Vector metrics in an adjusted model; removal of t cases with high TVOC levels slightly reduced t power of the Irritancy/PC metric, and reduced the statistical significance of the AF/CP Source Vector metric to predict irritancy symptoms to below the 90% level.

These results are from a single study and require further investigation and confirmation in other sets of buildings. The CHBS buildings were chosen to be representative of the typical office environment. However, 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 new methodology developed here to obtain an exposure metrics for a complex mixture of VOCs has linked low level VOC exposures from specific types of indoor sources to SBS symptoms for the first time. This methodology, when applied to other buildings and larger data sets, may be a useful tool in helping to determine some of the causes of SBS symptoms, and ultimately contribute to solutions to this problem.

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