Indoor Air 2008; 18: 156–170
www.blackwellpublishing.com/ina

INDOOR AIR
doi:10.1111/j.1600-0668.2008.00521.x

Outdoor ozone and building-related symptoms in the BASE study

Abstract Reactions between ozone and indoor contaminants may influence human health and indoor air quality. The U.S. EPA Building Assessment Survey and Evaluation (BASE) study data were analyzed for associations between ambient ozone concentrations and building-related symptom (BRS) prevalence. Multiple logistic regression (MLR) models, adjusted for personal, workplace, and environmental variables, revealed positive relationships ($P < 0.05$) between ambient ozone concentrations and upper respiratory (UR), dry eyes, neurological and headache BRS (odds ratios ranged from 1.03 to 1.04 per 10 $\mu g/m^3$ increase in ambient ozone concentrations). Other BRS had marginally significant relationships with ambient ozone ($P < 0.10$). A linear dose–response in UR symptoms was observed with increasing ambient ozone ($P = 0.03$); most other symptoms showed similar but not statistically significant trends. Ambient ozone correlated with indoor concentrations of some aldehydes, a pattern suggesting the occurrence of indoor ozone chemistry. Coupled with the MLR ambient ozone-BRS analysis, this correlation is consistent with the hypothesis that ozone-initiated indoor reactions play an important role in indoor air quality and building occupant health. Replication with increased statistical power and with longitudinal data is needed. If the observed associations are confirmed as causal, ventilation system ozone removal technologies could reduce UR BRS prevalence when higher ambient ozone levels are present.

M. G. Apte, I. S. H. Buchanan, M. J. Mendell
Lawrence Berkeley National Laboratory, Berkeley, CA, USA

Key words: Ozone Initiated Chemistry; Sick Building Syndrome; Aldehydes; Dose Response; Multiple Logistic Regression; National Ambient Air Quality Standard.

Michael G Apte, Ph.D.
Acting Group Leader
Commercial Buildings and Indoor Environmental Quality Group
Indoor Environment Department
MS: 90-3058
Lawrence Berkeley National Laboratory
1 Cyclotron Rd
Berkeley CA 94720, USA
Tel.: (510) 486-4669
Fax: (510) 486-6658
e-mail: mgapte@lbl.gov

Received for review 30 March 2007. Accepted for publication 12 January 2008.

Practical Implications
This paper provides strong statistical evidence that supports (but does not prove) the hypothesis that ozone entrained into buildings from the outdoor air is involved in increasing the frequency that occupants experience and a range of upper and lower respiratory, mucosal and neurological symptoms by as much as a factor of 2 when ambient ozone levels increase from those found in low-ozone regions to those typical of high-ozone regions. Although replication is needed, the implication is that reducing the amount of ozone entrained into building ventilation systems, either by ambient pollution reduction or engineered gas-phase filtration, may substantially reduce the prevalence of these symptoms experienced by occupants.

Introduction

Building-related symptoms (BRS), often also called sick building syndrome symptoms, are a set of health symptoms with unknown etiology that building occupants report when they are in a building, but that lessen when they leave or are away from the building (Hodgson, 2002; Levin, 1989). BRS include respiratory and mucosal effects as well as neurological symptoms such as headache and fatigue.

Although the causes of BRS are often unexplained, low ventilation per person rates (< 10 l/s per person) have consistently been associated with BRS (Seppänen et al., 1999). Seppänen et al. (1999) concluded in a review of the literature that ventilation rates of less than 10 l/s per person were associated with relative risks of 1.1–6 for BRS in occupants. Erdmann and Apte (2004) found in a large random survey of US office buildings that for every 100 ppm increase in indoor minus outdoor carbon dioxide concentrations (dCO_2) office workers experienced 8–23% increased odds of having certain mucous membrane or lower respiratory symptoms when in the buildings. These findings support the hypothesis that the indoor air quality of a building plays an important role in BRS.

One probable reason for association of low per-person ventilation rates with BRS is that they act as a

proxy or surrogate for increased levels of indoor air pollutants, such as volatile organic compounds (VOCs) generated by buildings, contents, or occupants. This is because provision of less outdoor air for the indoor environment leads to less dilution of air contaminants from indoor sources. Thus, first-order, lower ventilation rates imply potentially higher levels of indoor air pollutants, while high ventilation can increase the removal of these indoor contaminants (Levin, 1991; Weschler and Shields, 1987).

One factor that influences the indoor air contaminant load in buildings is chemical interactions and reactions between oxidizing agents and organic molecules found indoors, such as chemicals used as cleaners (Uhde and Salthammer, 2007; Weschler, 2004). One such oxidizing agent is ozone, an indoor contaminant with well-established links to morbidity and mortality (Lippmann, 1989; Weschler et al., 2006). The dominant source of indoor ozone involved in these reactions is ambient ozone that penetrates indoors (Weschler, 2000). In the absence of significant indoor sources, ozone concentrations tend to lag behind ambient ozone concentration and typically range from 10% to 50% of outdoor concentrations (Weschler, 2006). The indoor/ambient ozone is affected by multiple factors including ventilation rate, ozone residence time and deposition velocity (Lee et al.,1999), and limitations in availability of compounds that react quickly, reducing ozone concentrations. Removal of entrained ambient ozone occurs because it reacts with compounds on surfaces, in the air, and in building materials or equipment (Nazaroff et al., 2006; Weschler et al., 1992). Importantly, even though indoor ozone concentrations are reduced, people spend the majority of their day indoors; therefore a substantial proportion of a person's exposure to ozone occurs indoors (Weschler, 2006). Furthermore, health risks are increased not only by low-level chronic (long-term) exposure to ozone, but also by exposure to the irritating by-products of ozone reactions (Weschler, 2006). Recent studies have shown that the products of these reactions are often more irritating than their chemical precursors (Klenø and Wolkoff, 2004; Mølhave et al., 2005; Nøjgaard et al., 2005; Weschler and Shields, 2000; Wolkoff et al., 2006).

Reactions of ozone with certain organic molecules occurring indoors at certain concentrations can produce short-lived products that are highly irritating relative to the reaction precursors, and may also have long-term health effects (Destaillats et al., 2006; Nazaroff et al., 2006; Weschler, 2000; Wilkins et al., 2001; Wolkoff et al., 2000). Known products of indoor ozone reactions include compounds including formaldehyde, acetaldehyde, and other organic acids (see Weschler, 2006; Table 1 for thorough summary of ozone reaction products). Some of these compounds are known to cause ill health in humans (Weschler, 2006). Because of their potential irritancy, it is thought that many of these reaction by-products have a large impact on the overall indoor air quality of a building (Weschler, 2006; Wolkoff et al., 2006).

Mølhave et al. (2005) investigated the interaction between indoor ozone and household dust. Subjects exposed to dust (75 $\mu g/m^3$ of total re-suspended office dust) and ozone (300 ppb = 590 $\mu g/m^3$) treatments in climate-controlled chambers for 3 h had significantly ($P < 0.05$) reduced peak expiratory flow (a measure of respiratory function) when compared with subjects from the ozone-only or dust-only treatments. Subjects exposed to the dust–ozone treatment also reported a

Table 1 Pearson's correlations between various ozone concentration metrics calculated for the best available hourly ambient ozone data from the US EPA for each BASE building site

Ozone metric	Stat.	AM	2WK24H	WK24H	AVOZ	2WKWD	WKWD	WDOZ	LWDOZ
AM	*r* [a]								
annual arith. mean	*P* [b]	1							
2WK24H	*r*	0.681							
mean event week and 1 week and 1 week prior 24 h	*P*	<0.0001	1						
WK24H	*r*	0.605	0.930						
mean event week 24 h	*P*	<0.0001	<0.0001	1					
EVD24H	*r*	0.483	0.767	0.870					
mean event day 24 h	*P*	<0.0001	<0.0001	<0.0001	1				
2WKWD	*r*	0.622	0.932	0.877	0.710				
mean event week and 1 week prior, workday	*P*	<0.0001	<0.0001	<0.0001	<0.0001	1			
WKWD	*r*	0.565	0.866	0.932	0.788	0.936			
mean event week, work day (8–17)	*P*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1		
WDOZ	*r*	0.481	0.744	0.835	0.917	0.792	0.874		
mean event day, work day (8–17)	*P*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1	
LWDOZ	*r*	0.487	0.749	0.815	0.892	0.761	0.815	0.937	
mean event day, late afternoon (15–18)	*P*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1

Event week is the study week during the BASE study for each building.
Sample size is 100 in each case.
[a]Pearson correlation coefficient.
[b]Probability of no correlation.

significant increase in the 'feeling of dry eyes' ($P < 0.03$), 'feeling of sleepiness' ($P < 0.02$) and 'feeling of skin irritation' ($P < 0.02$) when compared with subjects in the other two exposure groups. These negative health symptoms (dry eyes, sleepiness and skin irritation) are similar to the symptoms that occupants report when they experience BRS, suggesting that indoor ozone chemistry may play a role in BRS. However, the challenge ozone concentrations were rather high, reducing the relevance to real-world conditions.

More recently Tamás et al. (2006), varied ozone and limonene concentrations in occupied test office spaces and found similar interactions as in the Mølhave et al. study. One of the most interesting findings from Tamás et al.'s study was that 40 ppb of limonene with no ozone did not affect the occupant's perception of the air quality of a room, but when ozone was added to the room with 40 ppb of limonene, such that ozone's residual concentration was 32 ppb (a typical urban indoor concentration), nearly half of the participants became dissatisfied with the indoor air quality. In addition, the combination of ozone and limonene resulted in greater sensory pollution loads (measured in Olfs) than either limonene or ozone alone. Although the short-term profile of exposures and responses in this experiment does not exactly match that of those of a work day, these results suggest that the interactions between ozone and limonene (and possibly other terpenes) can have a serious impact on the perceived indoor air quality during the work day, and may impact the health of occupants as well.

Other relevant human exposure studies reporting sensory response to ozone-initiated indoor chemistry are discussed in key reviews by Wolkoff et al. (2006), Weschler (2006) and Weschler et al. (2006). While these laboratory studies suggest that a relationship between ozone and ill health symptoms may exist, there is a lack of studies that have found the same association outside of the laboratory. Few, if any, field experiments or analyses of field data have been conducted to determine if such an association is detectable. Note however, a number of field studies have found associations that may be attributed to ozone chemistry (Höppe et al., 2003, Subramanian et al., 2000, Ten-Brinke et al. 1998) where insufficient information was available to make a clear connection. The analysis presented here attempts to identify relationships between ambient ozone and BRS using data obtained from office workers during the US EPA Building Assessment Survey and Evaluation (BASE) study of 100 US office buildings (EPA 2003).

We hypothesized that given the knowledge of indoor ozone-driven reactions and the potential physiological effects of the products of these reactions, increasing levels of ambient ozone would lead to higher prevalence of BRS among occupants within a building. This was predicted to occur through higher transfer rates of ozone into the indoors, increasing the quantity of irritating VOC oxidation products from ozone–VOC reactions indoors. It is known that the resulting reaction products may elicit sensory irritation in occupants exposed to them. It is expected that at sufficient levels of exposure to these contaminants the occupants would experience sensory irritation and possibly other health symptoms and that the symptoms would diminish with the removal of exposures, consistent with the definition of BRS.

Methods

Data

The data used in this analysis were gathered during the US EPA BASE study that took place from 1994 to 1998. Each of the 100 randomly selected office buildings was studied for 1 week either during the winter or summer. Mechanical ventilation systems were used in 98 of the buildings. The BASE study collected data on environmental factors (e.g. indoor and outdoor temperature, relative humidity, CO_2 concentrations, and selected VOCs), study space ventilation rates, building characteristics [e.g. heating, ventilation, and air conditioning (HVAC) system configuration and maintenance], workplace factors (e.g. cleaning schedules, cleanliness, occupant density), and personal factors (e.g. age, sex, medical conditions, smoking status, health symptoms). Personal data were collected via a confidential self-administered questionnaire distributed to the occupants. Further details of the building selection process and study methodologies have been discussed elsewhere in greater detail (EPA 2003; Womble et al., 1993, 1996).

Volatile organic compound concentrations were measured indoors at three locations in each study space. Sampling was conducted on the Wednesday of the study week and included workday (approximately 08:00–17:00 hours) time-weighted averages. Three sampling methods were employed to measure VOCs: dinitrophenyl hydrazine (DNPH) was utilized for formaldehyde and acetaldehyde while electropolished SUMMA® canisters and multisorbent tubes were used for the remaining compounds (see EPA 2003 for quantitation and quality assurance and control methods). Measurements of VOCs were conducted using multisorbent tubes selected preferentially; however, the BASE study did not use these tubes in the first years, and the analyte list was not consistent throughout the study. SUMMA® canister data were used only for compounds with measured analyte concentrations substantially above their respective limits of detection. Although some reactions between VOCs and oxidants such as ozone may have continued post-sampling,

within the canisters, by selecting canister-sampled compounds with relatively high concentrations the relative concentration change from these potential reactions was minimized.

Neither indoor nor ambient ozone concentration measurements were included in the original BASE study. The EPA acquired (blindly through a third-party contractor) contemporaneous ambient ozone concentration data from historical records of ambient air quality monitoring stations near the study buildings after the BASE study data collection was completed. The ozone data used were from the US EPA's national air monitoring (USEPA, 2007) network and were subject to full quality assurance and quality control measures required by that network. No information is available on the indoor ozone concentrations of the BASE study buildings.

Variables

This analysis uses the weekly definition of BRS utilized by previous studies which analyzed the BASE data (Apte et al., 2000; Erdmann and Apte, 2004). A health symptom was classified as building related if both of the following conditions were met: (1) the symptom occurred on at least 1 day/week during the 4 weeks prior to administration of the questionnaire and (2) the symptom got better when the occupant was away from his/her work environment. Both criteria were determined from occupant response to the self-administered questionnaire. The questionnaire was administered on the Thursday of the study week at each BASE building.

Four individual BRS were analyzed. Individual symptoms included: cough, dry eyes, dry/irritated skin, and headache. In addition, three aggregate BRS categories were constructed to more broadly assess symptom types: lower respiratory (LR), upper respiratory (UR), and neurological (NEURO). Aggregate BRS categories were defined as the presence of at least one of the respective symptoms: LR (wheeze, shortness of breath or chest tightness), UR (nose/sinus congestion, sore throat or sneeze), and NEURO (fatigue or trouble concentrating). Although these individual and aggregated symptoms are based on a 4-week recall, it is assumed that the recall is influenced by more recent symptom rates, most strongly by those occurring on the day of the questionnaire administration (Gendreau et al., 2003).

Four continuous variables were created from the hourly ambient ozone data for use in analyses. Hourly ambient ozone data from the day when the self-administered questionnaire was taken (typically Thursday) were used to construct a 24-h average concentration variable (AVOZ), an average workday (08:00–17:00 hours) concentration variable (WDOZ), and an average late workday (15:00–18:00 hours) concentration variable (LWDOZ). AVOZ, WDOZ, and LWDOZ were scaled by a factor of 10 to make interpretation of results more intuitive. Thus AVOZ, WDOZ, and LWDOZ have units of 10 $\mu g/m^3$. The fourth ozone variable, WEDOZ, consists of the workday (08:00–17:00 hours) ozone concentrations on the day when VOC monitoring occurred. Five additional ambient ozone variables with differing averaging time periods were constructed to study the temporal stability of the variables used in the analyses. These ozone concentration metrics are: AM (annual arithmetic mean ozone); 2WK24H (24-h mean event week and previous week); WK24H (24-h mean event week); 2WKWD (workday mean event week and previous week); and WKWD (mean event week workday). Logistic regression models of the BRS with AM as an independent variable were also constructed to investigate the sensitivity of these analyses to the temporality of the ozone metric.

Indoor VOC concentration data from three locations within each study space were averaged to obtain an average VOC concentration for each building. The choice of VOC data (canister or multisorbent) used in this analysis varied based on the individual compound and its sampling characteristics. The data selected for each compound were based on the sampling method which had the fewest concentration measurements below the sampling method's respective lowest detection limit, so that the best available information may be used. Preference was given to sampling methods that were consistent across as many buildings as possible. This was an issue because the specific VOC analytes were changed in the study protocol several times during the course of the BASE study, so that many of the compounds were not measured in all buildings.

Statistical methods

The statistical analyses reported in this study were conducted using SAS 8.2 software for Windows PC (SAS 1989) using established biostatistical methods (Kleinbaum et al., 1982; Selvin, 1995). Pearson's correlation coefficients and probabilities were calculated for the above-described ozone temporal metrics. The relationship between ambient ozone concentrations and BRS in the BASE study was analyzed using the SAS logistic procedure. We calculated odds ratios (ORs), Wald maximum likelihood (WML) statistics, 95% confidence intervals and *P*-values. Crude (unadjusted, bivariate logistic regression) and adjusted (multivariate logistic regression) models were constructed for each of the four individual symptoms and the three aggregate symptom categories. The explanatory variables of interest were AVOZ, WDOZ, and LWDOZ. Each explanatory variable was examined in a separate set of logistic regression models.

Adjusted logistic models were controlled for personal, environmental, and workplace factors that were

assumed to confound the BRS–ozone relationship. Covariates used in the adjusted models included occupant sex, environmental sensitivities (previously diagnosed dust allergy, mold allergy, hayfever, eczema, asthma, and migraine), age and smoking status, thermal exposure, indoor minus outdoor carbon dioxide concentration (dCO_2) as an indicator of ventilation per occupant, indoor relative humidity (RH), TMB (a tracer of outdoor automobile pollution), building heating and cooling degree days[1] (HDD and CDD, respectively), and the season in which the building was studied. Details of the selection process and methods of calculation for each of these variables can be found in Apte et al. (2000) and Erdmann and Apte (2004).

Each ambient ozone variable, in addition to inclusion in MLR models as single continuous variables, was also modeled in two alternate forms. A categorical variable for ozone, using dummy variables, represented five levels of exposure, to assess the dose–response relationship between ozone and BRS. The five categories represented quintiles of the ozone data, using the lowest quintile (bottom 20%) as the reference level. Finally, interval-level variables, with values of 1–5 representing the quintile categories, were used in the MLR models to determine the significance of an assumed linear dose–response relationship. The WML statistic and associated *P*-value for this interval-level variable were used as a measure-of-fit of the dose–response relationship for the adjusted categorical associations between ozone measures and BRS (SAS 1989).

To determine the possibility of ozone-initiated indoor chemistry, VOC concentrations were correlated with WEDOZ (averaged 1-h ambient ozone concentrations contemporaneous with the VOC sampling), and Pearson's correlation coefficients (*r*-values) were calculated. Compounds were eliminated if $r < 0.10$. This was done because with such a small *r*-value the magnitude of the relationship between ozone concentration and VOC concentration is negligible.

Results

Ozone data

Ambient ozone data were available for all 100 buildings in the BASE study; however, data were missing for Wednesday in one building. The distributions of the four continuous ozone variables are presented in Figure 1. The ranges for AVOZ, WDOZ, LWDOZ, and WEDOZ were 4.9–132, 4.9–169, 4.9–210, and 4.9–166 $\mu g/m^3$, respectively. The mean values for each variable were 50, 67, 71, and 66 $\mu g/m^3$, respectively. The average AM ozone concentration was 49 ± 11 $\mu g/m^3$ (range 27–71 $\mu g/m^3$). Only one building had its workday average ambient ozone concentration (WDOZ) greater than 157 $\mu g/m^3$ [80 ppb, the 8-h National Ambient Air Quality Standard (NAAQS)]. Table 1 shows a Pearson's correlation matrix for the calculated temporal ozone metrics, ordered roughly from the longest averaging period to the shortest averaging periods. Correlations ranged from 0.94 to 0.49 with *P*-values consistently less than 0.0001. Correlations between workday average ozone metrics for event days and those for single or 2 weeks were very high, indicating that ozone variability from the event day to previous days was low and that the event-day metrics were suitable for use in regression models against the symptoms reported with a 4-week recall period.

Study population

Building occupants returned over 4200 questionnaires, which corresponded to a response rate of about 85%. The majority of respondents were female (66%), nonsmokers (85%), over the age of 40 years (55%) and had at least one doctor-diagnosed or self-reported sensitivity to the environment (81%). Environmental and workplace parameters were described fully by Erdmann and Apte (2004).

Using data from the questionnaires and the BRS definition, the prevalence of the four individual BRS ranged from 4.7% to 18.6%, while that for the three aggregate BRS categories from 4.2% to 21.0% (Table 2).

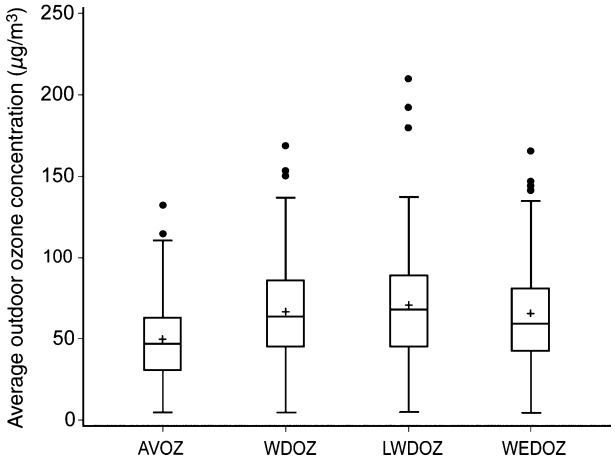

Fig. 1 Distribution of the four continuous ozone variables. The large box represents the inter-quartile range (IQR), the '+' is the mean, while the horizontal line dividing the box is the median. The upper and lower whiskers represent the 1.5 times the IQR above the 75th percentile and below the 25th percentile, respectively, and the solid dots are values above the upper whisker

[1]Heating degree-days and cooling degree-days are calculated over a year by adding up the differences between each day's mean daily temperature and the temperature of 18°C (or 65°F), above or below which the building is assumed not to need any heating or cooling, respectively.

Table 2 Number of respondents to survey questions (*n*) and the prevalence of BRS symptoms in the 100 building BASE study

BRS	*n*	Prevalence (%)
LR	4318	4.2
Cough	4260	5.1
UR	4308	21.0
Dry Eyes	4245	18.6
Neurological	4313	19.2
Dry Skin	4201	4.7
Headache	4249	15.2

Ozone–BRS logistic regression results

In order to assess temporal sensitivity of the regression models to ozone metrics, the seven BRS metrics used in this study were regressed against annual arithmetic mean (AM) ozone concentrations. These models yielded odds ratios uniformly above unity. The only unadjusted odds ratios (OR) with value less than unity was cough, and the UR symptom OR was 1.1 per 10 $\mu g/m^3$ ($P = 0.009$). All adjusted BRS AM models had ORs above unity, and both UR and Dry Eye symptoms were statistically significant with ORs of 1.18 and 1.11 per 10 $\mu g/m^3$ ($P < 0.05$), respectively.

Results from further logistic regression analyses are presented in Tables 3–5. Crude and adjusted ORs along with their 95% confidence intervals and *P*-values from the AVOZ and WDOZ analysis are presented in Tables 3 and 4, respectively. Model results were very similar for these ozone variables. Of note is that in crude and adjusted models, for both ozone variables, the odds ratios were consistently above unity for all BRS excepting 'Dry Skin'. In the crude models, UR and NEURO had significant ($P < 0.05$) positive relationships with outdoor ozone concentrations. After adjusting the models for personal, environmental, and building characteristics, only UR remained significantly associated with ambient ozone at the 95% confidence level and *P*-values for LR and dry eyes were 0.06 and 0.09, respectively.

Table 3 Crude and adjusted association per 10 $\mu g/m^3$ between 24-h ozone (AVOZ) and BRS including ORs, 95% confidence intervals and *P*-values

	Crude models			Adjusted models		
BRS	OR	95% CI	*P*-value	OR	95% CI	*P*-value
LR	1.04	0.99–1.1	0.14	1.07	1.00–1.15	0.06
Cough	1.02	0.97–1.07	0.52	1.05	0.99–1.12	0.12
UR	**1.03**	**1.01–1.06**	**0.02**	**1.04**	**1.01–1.08**	**0.02**
Dry eyes	1.02	1.00–1.05	0.11	1.03	1.00–1.07	0.09
NEURO	**1.03**	**1.00–1.06**	**0.05**	1.03	0.99–1.07	0.16
Dry Skin	0.97	0.92–1.03	0.29	0.99	0.92–1.06	0.74
Headache	1.03	1.00–1.06	0.08	1.03	0.99–1.08	0.13

Statistically significant associations ($P < 0.05$) given in bold.

Table 4 Crude and adjusted association per 10 $\mu g/m^3$ between workday ozone (WDOZ) and BRS including ORs, 95% confidence intervals and *P*-values

	Crude models			Adjusted models		
BRS	OR	95% CI	*P*-value	OR	95% CI	*P*-value
LR	1.03	0.99–1.07	0.14	1.05	0.99–1.1	0.10
Cough	1.01	0.97–1.05	0.56	1.04	0.99–1.09	0.12
UR	**1.02**	**1.00–1.04**	**0.05**	**1.03**	**1.00–1.06**	**0.03**
Dry eyes	1.02	1.00–1.04	0.11	1.02	1.00–1.05	0.10
NEURO	**1.02**	**1.00–1.04**	**0.06**	1.02	0.99–1.05	0.19
Dry Skin	0.98	0.94–1.02	0.21	0.99	0.94–1.04	0.65
Headache	1.02	1.00–1.04	0.13	1.02	0.99–1.05	0.18

Statistically significant associations ($P < 0.05$) given in bold.

Table 5 Crude and adjusted association per 10 $\mu g/m^3$ between late workday ozone (LWDOZ) and BRS including ORs, 95% confidence intervals and *P*-values

	Crude models			Adjusted models		
BRS	OR	95% CI	*P*-value	OR	95% CI	*P*-value
LR	1.03	1.00–1.06	0.08	1.04	1.00–1.08	0.09
Cough	1.02	0.99–1.05	0.23	1.03	0.99–1.07	0.11
UR	**1.03**	**1.01–1.05**	**<0.001**	**1.04**	**1.02–1.06**	**0.001**
Dry eyes	**1.02**	**1.01–1.04**	**0.01**	**1.03**	**1.01–1.05**	**0.01**
NEURO	**1.03**	**1.01–1.05**	**0.002**	**1.03**	**1.01–1.05**	**0.02**
Dry Skin	0.99	0.95–1.02	0.37	0.99	0.95–1.04	0.79
Headache	**1.02**	**1.00–1.04**	**0.03**	**1.03**	**1.00–1.05**	**0.04**

Statistically significant associations ($P < 0.05$) given in bold.

The estimates from the LWDOZ analysis (Table 5) show more statistically significant elevations. In the crude models, significant ($P < 0.05$) ORs for UR, cough, dry eyes, NEURO, and headache BRS ranged from 1.02 to 1.03 per 10 $\mu g/m^3$. In the adjusted models UR, dry eyes, NEURO and headache were significant at the 95% confidence level. LR was found to be marginally significant ($P = 0.09$). Although the LWDOZ point estimate ORs are identical to or even lower than for AVOZ, the confidence intervals are narrower, making LWDOZ more significant. This observation is discussed below.

Dose–response analysis

Figure 2 shows estimates for associations of the categorical levels of ozone, and the *P*-values for trend in dose–response, for LWDOZ and BRS after adjustment for personal, workplace, and environmental factors. LWDOZ had the strongest and most significant relationship to BRS, and hence its dose–response results are presented here. Visually LR, UR, dry eyes, and headache seem to indicate increasing odds of symptom response as ozone concentration increases; however, one of the ozone-level ORs for each symptom deviated from the expected pattern. The results of the interval-level ozone variable MLR that was used to test for significance of a linear trend indicate, however, that only UR had a significant ($P < 0.05$) linear dose–response relationship with LWDOZ.

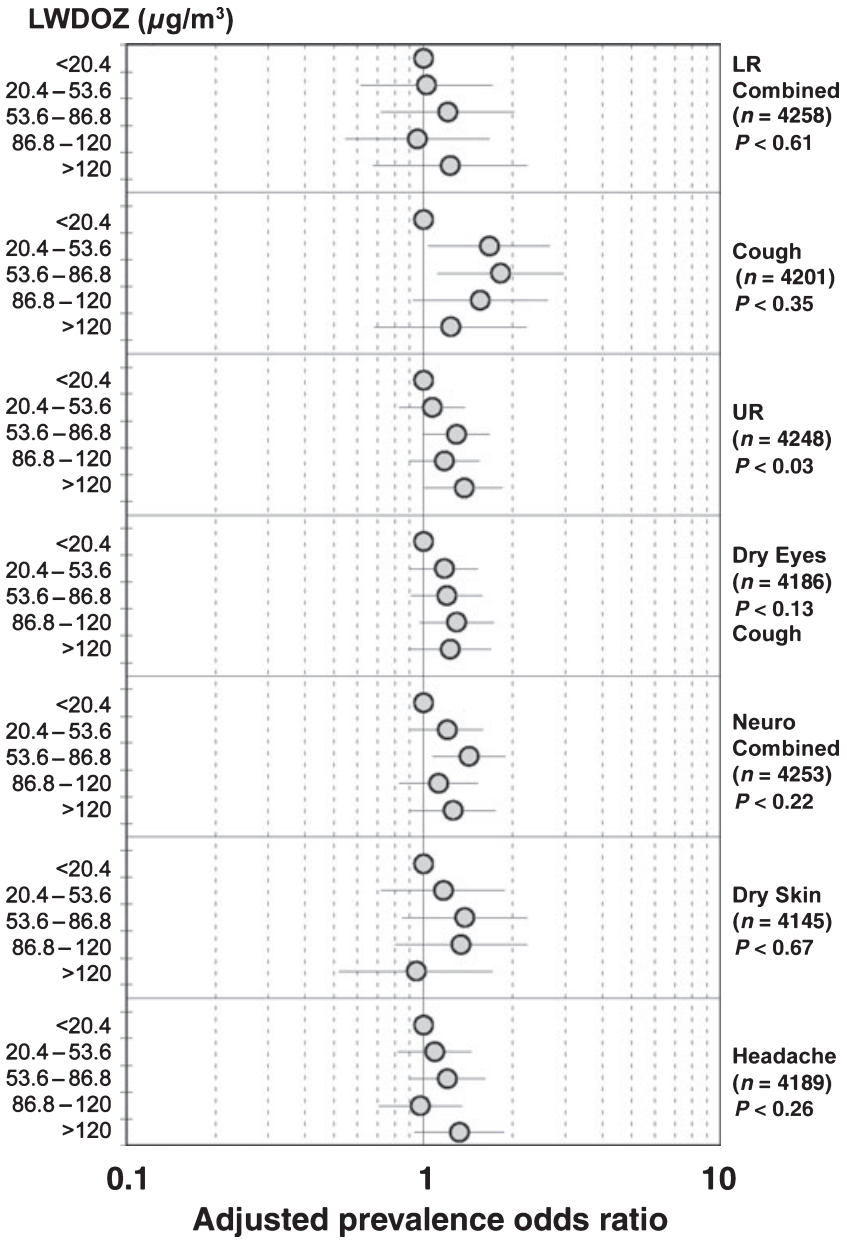

Fig. 2 Dose–response graph for late workday (15:00–18:00 hours) ambient ozone concentrations (LWDOZ). ORs and their 95% confidence interval are shown for each of the BRS symptoms at the given LWDOZ concentrations, relative to the lowest ozone exposure cohort (< 20.4 $\mu g/m^3$). N is the sample size in the models. The *P*-values were obtained assuming a linear dose-response relationship between LWDOZ and BRS in a MLR model using a single five-part categorical ozone variable that represented the five ozone ranges on the left of the figure

Covariates in adjusted models

For completeness it is necessary to include information on the statistical associations between the model covariates and the BRS outcome. Many of the covariates had significant ($P < 0.05$) relationships with the BRS symptoms. The magnitude of the ORs and their significance were similar between the three sets of models. Using the LWDOZ models as an example, the statistically significant relationships between the covariate and the respective symptoms are summarized in Table 6. The behavior of covariates 'Season', and 'dCO_2' in the models is of interest and is discussed below.

VOC and ozone correlations

The WEDOZ–VOC correlation analysis included a total of 40 compounds. The number of buildings in which specific VOCs were sampled ranged from 13 to 100 depending upon the compound because the VOC analysis protocols changed during the study. All but one building had ozone data for Wednesday; therefore the maximum sample size in the analysis was 99

Table 6 Associations between BRS symptoms and covariates in the LWDOZ multivariate logistic regression models

Covariate	Units	OR range ($P < 0.05$)	BRS variables with $P < 0.05$	OR >1 ($P > 0.05$)
Season[a]	Winter relative to summer	**1.27–1.53**	Cough, UR, dry eyes and headache	LR, NEURO, dry skin
Sex		**1.79–2.89**	All symptoms	
Age	40+ years relative to <40	**1.19–1.42**	LR, cough and dry eyes	UR, NEURO, dry skin
d(CO_2)	Per 100 ppm	**1.08**	UR	LR, dry eyes, NEURO, dry skin
Smoking status	Current smoker relative to non-smoker	**1.27–1.87**	LR, UR, NEURO, and headache	cough, dry eyes, dry skin
Environmental sensitivities	Sensitve[b] relative to not sensitive	**1.59–4.83**	All symptoms	
CDD	°C-days	**0.98**	UR and dry eyes	headache
HDD	°C-days	**0.97**	LR	headache
Relative humidity	RH <20%			LR, UR, dry skin
TMB	ppb	**1.18**	Dry skin	LR, UR, cough, dry eyes, NEURO, and headache
Thermal exposure	Per 10°C-h above 20°C			cough, dry eyes, NEURO, dry skin

[a]See discussion in text.
[b]Presence of at least one doctor-diagnosed or self-reported environmental sensitivity including dust allergy, mold allergy, hayfever, eczema, asthma, and migraine.

buildings. VOC–ozone correlations for four compounds analyzed from canister samples are slightly more likely to be underestimated because of possible post-sampling oxidant-initiated reactions. However, in the case of D-limonene, samples from 70 buildings were analyzed using both multsorbent and canister methods and the two sample methods were highly correlated ($r^2 = 0.92$, slope = 0.97, intercept = −0.04), suggesting that this terpene was reliably sampled and quantitated using both methods. Table 7 shows Pearson's correlation results for the 20 VOCs with $r \geq 0.10$. Nonanal was most strongly associated with increasing ambient ozone ($r = 0.60$; $P < 0.0001$). To aid the reader, the table also identifies whether the VOCs are saturated and whether they contain a carbon–oxygen double bond because compounds with these characteristics are created through ozone-initiated chemistry.

Table 7 Ozone and VOC correlation analysis results ($R \geq 0.10$), sorted by saturation, presence of a carbon–oxygen double bond and *r*-value

Compound	*r*	*n*	Saturated	C=O	Sampling method
Formaldehyde	0.18*	99	N	Y	DNPH
Acetaldehyde	0.28**	85	N	Y	DNPH
Pentanal	0.40**	40	N	Y	Multisorbent
Hexanal	0.38**	40	N	Y	Multisorbent
Nonanal	0.60***	40	N	Y	Multisorbent
Ethanol	0.49*	13	Y	N	Canister
1-Butanol	0.38**	40	Y	N	Multisorbent
2-Ethylhexanol	0.25	40	Y	N	Multisorbent
Phenol	0.26	40	N	N	Multisorbent
2-Butoxyethanol	0.32**	40	Y	N	Multisorbent
Ethyl Acetate	0.12	69	N	Y	Multisorbent
TMPD-(MIB &DIB)[a]	0.32**	40	N	Y	Multisorbent
TXIB[b]	0.19	40	N	Y	Multisorbent
n-Undecane	0.11	86	Y	N	Canister
Benzene	−0.29**	69	N	N	Multisorbent
o-Xylene	−0.12	69	N	N	Multisorbent
Ethylbenzene	−0.19	69	N	N	Multisorbent
Naphthalene	0.13	69	N	N	Multisorbent
D-Limonene	0.11	99	N	N	Canister
Chloromethane	0.24**	86	Y	N	Canister

*$P < 0.10$; **$P < 0.05$; ***$P < 0.0001$.
[a]TMPD-MIB = 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate.
[b]TMPD-DIB = 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Other aldehydes (acetaldehyde, pentanal, and hexanal), as well as 1-butanol, the TMPD (2,2,4-trimethyl-1,3-pentanediol) isomers, 2-butoxyethanol, and chloromethane were also positively associated with increasing ambient ozone ($P < 0.05$). In contrast, benzene, ethylbenzene and *o*-xylene were negatively associated (of these, only benzene had a *P*-value < 0.05).

Discussion

While the above logistic regression results do not demonstrate causality, they show that increased ambient ozone concentrations are consistently associated with the reporting of certain BRS symptoms in office workers. In all three sets of ozone models the consistency of the ORs exceeding 1 (given the null hypothesis of no relationship) suggests a robust positive association between ozone and some BRS, and a study that is too small to clearly detect this association for several other symptoms.

An issue of temporality exists because the BASE survey BRS questions related to frequency of symptoms over the previous 4 weeks, while the ozone metrics that showed the strongest relationships to self-reported BRS were temporally close to the day of symptom data collection. As discussed above, a reasonably strong correlation exists between all the ozone averaging metrics. The annual arithmetic mean ozone concentration had associations with the BRS very similar to those found in the more time-specific models. Although the symptom survey questions were based on a 4-week recall, the likelihood of recall bias toward more recent symptom experiences, as discussed in Gendreau et al. (2003), provides additional assurance that ozone measurements on the day of questionnaire administration are appropriate for these analyses.

The observation that a lack of statistical power exists is underscored when we look at LR and cough. Building-related LR and cough generally have much lower prevalence in office workers (here 4.2% and 5.1%, respectively) than those symptoms that had

statistically significant relationships with ozone (e.g. UR, eyes, NEURO, headache, with prevalences here ranging from 15% to 21%). LR and cough, despite increased ORs of the same magnitude as the outcomes with low *P*-values, had *P*-values ranging from 0.06 to 0.12 and were not significant at $P < 0.05$ in any of the adjusted models. Outcomes with only 5% prevalence require larger sample sizes to detect a significant difference at the 95% confidence level, and thus the study was underpowered to detect ORs of the size seen. To study these outcomes, a larger sample size of building occupants or a more sensitive outcome measure will be necessary in future studies.

Ozone data

It should be noted that the distance from each BASE building to the corresponding ambient ozone-monitoring station varied from less than 0.5 km to over 300 km. This was because many of the buildings studied in the winter season were nearest to ozone-monitoring sites that did not record hourly ozone concentrations in the winter. In this case the next nearest hourly monitoring site that was collecting data was used. When the logistic regression models presented here were redone using only data from ozone-monitoring stations that were less that 24 km from the buildings (a natural cut point given the distribution of the distances from ozone-monitoring site to their respective buildings), no major changes in the observed associations occurred. Therefore, in order to be more representative of the entire BASE dataset and of the United States office building stock as a whole, the analyses using all of the data are presented here. Future studies should ensure that local ambient and indoor ozone monitoring is included.

That only one building in these analyses experienced WDOZ concentrations greater than the NAAQS has major implications for the relevance of the findings in this study. First, the ambient ozone conditions are typical of those experienced in the US. Second, as the analyses are based on ozone concentrations that are low relative to the NAAQS, the observed risks are based on conservative conditions. Third, the results suggest that the NAAQS may not be low enough to protect against BRS across much of the US.

MLR results

When interpreting the ORs in these analyses, it is important to realize that they estimate the average increase in odds of BRS for every 10 $\mu g/m^3$ increase in ambient ozone concentrations, assuming that the ozone/BRS relationship is linear and causal. The observed ORs translate into roughly a 3–4% increase in BRS risk for every 10 $\mu g/m^3$ increase in ambient ozone concentration. If one considers the large range of ozone concentrations in this analysis (AVOZ: 127 $\mu g/m^3$, WDOZ: 164 $\mu g/m^3$ and LWDOZ: 205 $\mu g/m^3$) a 3–4% increase in the odds of having BRS per 10 $\mu g/m^3$ increase in ozone becomes a very large increase in overall odds for occupants in those buildings with high ambient ozone concentrations. Using the LWDOZ analysis as an example, with the occupants of buildings with the mean ozone concentration (71 $\mu g/m^3$) as the referent, those in buildings with the highest ozone concentration (210 $\mu g/m^3$) have an effective increase in odds of 68%, 49%, 49%, and 43% for having UR, dry eyes, neurological, and headache BRS, respectively. If one now uses the occupants from the lowest ozone 'exposure' buildings as the reference group, the odds of occupants in the highest ozone 'exposure' buildings having BRS increases substantially by 114%, 80%, 80%, and 69% for UR, dry eyes, neurological, and headache, respectively.

Continuing to use the LWDOZ models as examples and using the percent risk reduction (PRR) calculation, as done in Erdmann and Apte (2004) Apte et al. (2000), we can estimate the percentage of BRS that office workers suffer that is due to increased ambient ozone concentrations. These PRR analyses assume that the findings in this study are repeatable with similar results in new research. The PRR calculations suggest that, if reductions were made in ambient ozone levels entrained into the building to the lowest level observed in the BASE study (4.9 $\mu g/m^3$), one could expect to see a 48%, 35%, 35% and 33% reduction in UR, dry eyes, NEURO, and headache BRS, respectively. These reductions assume that the relationship between ozone and BRS is causal and that all other factors are held constant while ozone reductions are made. This potential to cause large reductions in the BRS indicates another large benefit from reducing ambient ozone concentrations. More practically, reducing the amount of ambient ozone that enters into the indoor environment may be a viable alternative. The latter can be accomplished using various types of carbon-based filter technologies or absorbent filter materials (Gundel et al., 2002; Kelly and Kinkead, 1993; Shair, 1981; Shields et al., 1999).

It is interesting to find that the strongest and most significant relationships between ozone and BRS were in the model using late workday concentrations of ambient ozone. Although a very complicated and variable set of physical and chemical processes are at play in buildings, in general terms, exposures to products of indoor chemistry are expected to peak shortly after ozone levels reach their peak and this typically occurs in the late afternoon. The LWDOZ data reflect the concentrations at this time period. The lack of statistical significance in the LR, cough, and skin models is likely due to the low prevalence of these symptoms.

Dose–response

The dose–response analysis for LWDOZ presented in Figure 2 showed somewhat noisy point estimates and confidence intervals, but this is expected because of the reduction of power caused by dividing the data into quintiles. However, even with this reduction in power, a dose–response trend appears to be present for several of the symptoms and a linear dose–response trend is significant for UR. The fact that only UR had a significant *P*-value should be taken into perspective as this value was obtained under the assumption that the dose–response relationship is in fact linear on the logarithmic scale of ORs. The lack of significant dose–response relationships for other symptoms and the nonlinear dose–response patterns for some symptoms may indicate a more complex dose–response behavior for ozone and BRS, or may merely indicate the need for greater statistical power. Both considerations should be kept in mind, so that future studies or analyses do not assume that ozone and BRS have a linear relationship.

Covariates in model

Results from the MLR models suggest that BRS prevalence is greater during the winter. This may be due to misclassification of seasonal conditions (such as colds or influenza), or may be an indicator of another, undetermined environmental/seasonal risk factor for BRS. As with other BRS studies, females had increased risk of BRS when compared with males. It is unknown if this has anything to do with reporting bias, or biological differences, or differences in jobs or work environments. The most noteworthy personal risk factor for BRS in the models was the environmental sensitivity variable, indicating that occupants who had doctor-diagnosed or self-reported environmentally mediated illnesses, such as asthma, allergies, or sensitivity to tobacco smoke, were at substantially increased risk of having BRS.

One of the most interesting findings that emerged during the examination of the covariates in the MLR models was the lack of significant relationships between dCO_2 and BRS symptoms (with the exception of UR). Previous studies (Apte et al., 2000; Erdmann and Apte, 2004) have found statistically significant links between increasing levels of indoor minus outdoor CO_2 and combined mucous membrane (UR), dry eyes, sore throat, nose/sinus, sneeze, and wheeze BRS. The BRS definitions in that study were very similar, and in some cases identical to those in the current analyses (Table 8). It was argued that increased dCO_2 was proportional to lower per-person ventilation rate, and in turn, to increasing levels of indoor air contaminants. It was inferred that the inverse association of ventilation with symptoms was because ventilation removed indoor air contaminants that were causing symptoms. However, this model is complicated because increasing ventilation increases the transport of ozone from outdoors, while at the same time it shortens the age of air in the buildings and limits time for ozone-initiated reactions to proceed to completion. Additional study is required to better understand the impact of ambient ozone entrainment into buildings on the relationship between dCO_2 and symptoms.

Table 8 Adjusted association between indoor–outdoor CO_2 (dCO_2 per 100 ppm) and BRS in the BASE data

	dCO_2 ozone excluded		dCO_2 ozone included	
BRS	OR	95% CI	OR	95% CI
LR	**1.16**	**1.02–1.32**	1.11	0.97–1.27
Cough	1.03	0.91–1.17	0.99	0.87–1.14
UR	**1.13**	**1.06–1.21**	**1.08**	**1.01–1.16**
Dry eyes	**1.09**	**1.02–1.17**	1.06	0.98–1.14
NEURO	1.04	0.97–1.12	1.01	0.93–1.09
Dry Skin	1.06	0.94–1.21	1.07	0.93–1.23
Headache	1.03	0.95–1.11	1.00	0.92–1.08

Statistically significant associations ($P < 0.05$) given in bold.

Winter season, after controlling for ozone and other covariates in the model, had ORs for BRS consistently greater than unity, indicating significant, 27–53% increased prevalence of cough, UR, dry eyes and headache. All non-significant symptoms also had ORs > 1. When the ozone covariate was excluded from the multivariate models, the SEASON variable was only weakly associated with BRS (data not shown), with ORs that ranged from about 0.99 to 1.3 with no clear pattern related to symptom class. Only the UR symptoms were statistically significant (OR = 1.23, $P = 0.02$). Addition of the ozone variable appears to adjust for the seasonal variability of ozone-related effects such that an additional, unexplained winter season effect, is now visible.

VOC–ozone correlations

The result of the WEDOZ–VOC correlation should be viewed as qualitative in nature. This is because there was such variation in the sample size between different VOCs, and because variation in the sources of VOC makes the detection of such a relationship between ozone and certain VOC difficult given the experimental methods employed in the BASE study (i.e. post-study collection of ambient ozone data, no data on indoor ozone concentrations and no real-time VOC concentration data). In other words, one should primarily concentrate on the direction of the association (positive or negative) and the magnitude of association.

The VOC correlation analysis supplies evidence supporting (although not proving) that ozone chemistry takes place and may be contributing to the observed

prevalence of BRS in the buildings. In the absence of ozone chemistry, one would expect the indoor concentration of VOCs in the study buildings to vary randomly, without correlation with the indoor or ambient ozone concentrations. Of interest, formaldehyde acetaldehyde, pentanal, hexanal, and nonanal, which are known products of indoor ozone chemistry, have fairly large, positive *r*-values, indicating that the relationship between ozone and these compounds tracks together in a positive direction (Wolkoff et al., 2000, 2006). The association between ambient ozone and nonanal is particularly strong, consistent with expectations (Morrison et al., 1998). Thus with increasing ozone concentrations, and therefore increased ozone reactions with unsaturated hydrocarbons, we would expect to see an increase in aldehyde production, which we do.

Although the suggested presence of ozone-initiated reaction products is indicated by the correlations between ambient ozone and measured aldehydes, it is possible that other co-reaction products that were not measured contributed to the reported BRS. This is particularly important because evidence of the irritancy of the measured compounds is expected to emerge as more sensitive and responsive methods with real-time resolution are applied, better and routine characterization of these reaction intermediates may be possible (Nøjgaard et al., 2007).

Another aspect of the putative association between ozone-initiated chemistry and BRS relates to reaction product odor. This paper has focused primarily on the hypothesis that the BRS effects are elicited through the irritancy of reaction products at target tissues. However, many VOCs, particularly aldehydes, have odor thresholds well below their irritancy level, and subjective relationships between compound odor annoyance contributing to the perception of sensory irritation may confound true sensory irritation (Dalton, 2003). It is not possible to distinguish between subjective and true chemosensory irritation from the BASE study questionnaire. However, both types of irritation are likely to have an effect on building occupants' sense of health and well-being.

Interestingly, the unsaturated VOCs without carbon–oxygen double bonds measured in the study were not observed to have negative correlations with ozone as might be predicted. For example, D-limonene, a compound well characterized for its reactions with ozone indoors, has a positive and non-significant correlation with ozone. This lack of observation of negative correlation for this compound may simply be due to its relative abundance across the BASE buildings, such that small reductions caused by reactions are not resolved. Another explanation may be found in the observations of Subramanian et al. (2000) that limonene was found to be positively correlated with automobile exhaust chemicals including aromatic compounds. These compounds are precursors to ambient ozone production, suggesting that ambient ozone may be positively correlated with increased ambient D-limonene. The complexity of these competing reactions is beyond the scope of this statistical analysis. Finally, the lack of correlation may be due to some unexplained VOC sampling artifacts.

Three compounds, benzene, ethylbenzene and *o*-xylene, are all present in motor vehicle exhaust. In many cases outdoor-to-indoor transport is the major source of these compounds in indoor air. Motor vehicle exhaust also contains nitric oxide (NO), which reacts very quickly with ozone in the gas phase (Weschler and Shields, 1994). The observed negative correlations of benzene, ethylbenzene and *o*-xylene with ozone may reflect the co-occurrence of these compounds and NO (a sink for ambient ozone) in motor vehicle exhaust. Unfortunately, NO was not measured in the BASE study so this hypothesis cannot be verified by examining for a negative correlation between ozone and NO.

A prior analysis (Apte and Erdmann, 2002) of the BASE data examined the relationships between specific VOC concentrations and BRS symptoms and found no consistent trends. In logistic regression analyses, no clear patterns of relationships or trends between individual VOC concentrations and BRS were found with the exception of D-limonene. In these prior analyses, the ORs for D-limonene were statistically significant ($P < 0.05$) for four of the six symptoms and ranged from 0.91 to 0.97 per ppb, indicating that increasing levels of D-limonene were protective against BRS (or conversely, that decreasing level of D-limonene increased occupants' risk of BRS). These observations are contrary to those reported by Subramanian et al. (2000), who observed that the mean number of symptoms increased with D-limonene concentrations; however, the methods of symptom data collection and analysis were not described. One cause of decreased levels of D-limonene is reactions of D-limonene with ozone. Thus increased D-limonene concentrations may appear protective because they indicate fewer ozone–D-limonene reactions, and therefore fewer harmful reaction products indoors. The complexities of ozone-initiated alkene reactions and their downstream health effects cannot be resolved within the framework of the present statistical analyses.

Analysis and statistical limitations

While the results of the analyses presented here lend support to the hypothesis that ozone chemistry affects the prevalence of BRS, the limitations of the cross-sectional study design limits any causal conclusions. However, prior information on biological and physical

mechanisms lends plausibility to the hypothesis of a causal link between ozone and BRS. From a biological perspective, studies have shown that the interaction and reaction of ozone with indoor pollutants can increase negative odors indoors (Knudsen et al., 2003; Tamas et al., 2006) and may reduce study participants' respiratory function (Mølhave et al., 2005). Physically, studies have shown that harmful reaction products are produced from ozone reactions with indoor pollutants (Destaillats et al., 2006; Klenø and Wolkoff, 2004; Nazaroff et al., 2006; Nøjgaard et al., 2005; Weschler et al., 2006; Wolkoff et al., 2006). These observations support the need for further studies to establish if there is a causal link between ozone and BRS.

In addition, the use of ambient ozone data collected at varying distances from the study buildings limits the accuracy of results, as does the absence of indoor ozone data. One important element that should be incorporated into future studies is the collection of detailed real-time data on specific VOCs whose increase or decrease in concentrations can be used to trace ozone oxidative chemistry and whose indoor sources are known and well understood (e.g. Weschler et al., 1992). This will enable researchers to track the interrelationship between ozone concentrations, VOC concentrations, and the prevalence of BRS within a study space.

While questionnaire data on symptoms and other personal variables were collected at the individual level, environmental variables for each individual were based on study space averages. The VOC values assigned to each study participant are thus inexact, and by contributing measurement error, tend to lead to underestimates for any risk factors. More detailed studies which attempt to classify actual individual-level exposure to environmental variables would be needed to remove this source of possible bias, but this would involve tremendous costs if current exposure assessment methods are used. A related statistical limitation of this study comes from the study design itself. Study space averages or study space-level data for all environmental variables were applied to each occupant, but the analyses used the individual occupant as the unit of analysis. Thus the individual-level observations included in the statistical models are not truly independent from each other, because the working environment was shared by all study occupants within each building. Moreover, occupants within each building may be more correlated with each other than with those in other buildings, in ways not accounted for in logistic regression models. In general, analyzing such data as if individuals were fully dependent will result in some overestimation of the true precision of estimates. Prior analyses of BASE data using generalized estimating equations to adjust for these potential correlations, however, have shown that the effects on precision are minimal (Mendell et al., 2006).

Emerging areas of interest

Continued study is needed to fully explore the role that ozone indoor chemistry plays in BRS. One emerging area is the interaction of ozone and ventilation air filters in the mechanical ventilation systems of buildings. Ozone that is present in the air must pass through an air filter when entering the HVAC system from outdoors and when being recirculated indoors. This provides a surface where chemical reactions can occur. A recent study using used air filters found reductions in downstream ozone concentrations (Beko et al., 2006; Zhao et al., 2007), indicating that ozone was being destroyed on or in the filter itself. A new facet to this line of research explores what effect the type of filter medium has on BRS within a building (Buchanan et al., 2008). An interaction between ozone and air filters may help to further explain the causes of BRS in the workplace.

Reducing indoor ozone reduces the amount of BRS in a building, and new studies suggest that reduction of even low levels of chronic exposure to ozone may reduce overall mortality rates (Bell et al., 2006). Thus, although more research is needed, indoor mitigation and reduction of ozone may serve a dual purpose: reduction of BRS and the reduction of direct ozone-mediated mortality. Although replication of this study is necessary, findings of this study strengthen the argument for controlling the entry of ozone into the indoor environment. Such measures would be most helpful, in locations where outdoor environments have elevated ozone concentrations, in preventing high levels of ozone from entering into buildings through HVAC systems. Such measures were discussed briefly in Weschler et al. (2006), and may include both enhanced filtration in mechanical ventilation systems and scheduling strategies for both mechanical and natural ventilation systems. Carbon filters have been shown to be continuously effective, for over 3 years (Weschler et al., 1994) or even longer (Weschler et al., 2006), at removing large fractions of ozone from incoming ventilation air when sufficient carbon was employed.

Overall results

Overall, the analyses of ambient ozone associations with BRS in the BASE study data generated the following information.

- Only one of the 100 BASE buildings had daytime ambient ozone levels in excess of the US EPA NAAQS of 157 $\mu g/m^3$ during the study.
- In both crude and adjusted models, the ORs for ozone were consistently above unity for all BRS excepting 'Dry Skin'.

- BRS were most strongly associated with ambient ozone averages that included the late workday time period.
- When comparing the BRS risk for occupants of buildings with the mean level of LWDOZ (71 $\mu g/m^3$) to risk for those in buildings with the highest observed ozone concentration (210 $\mu g/m^3$) an increased odds of 68%, 49%, 49% and 43% for having UR, dry eyes, neurological, and headache BRS, respectively, was found.
- Likewise, when comparing the BRS risk for occupants of buildings with the lowest observed LWDOZ to those in buildings with the highest observed ozone concentration, the risk of having BRS increases substantially, to 114%, 80%, 80%, and 69% for UR, dry eyes, neurological, and headache symptoms, respectively.
- By reducing ambient ozone levels entrained into buildings to the lowest level observed in the BASE study (4.9 $\mu g/m^3$), one might (if associations observed here were causal) expect to see a 45%, 35%, 35%, and 33% reduction in upper respiratory, dry eyes, neurological, and headache BRS, respectively.
- BRS risks appear in many cases to have a dose–response trend with increasing ambient ozone levels. The upper respiratory symptom group was observed to have a linear and statistically significant trend of increasing symptom prevalence with increasing ambient ozone levels.
- Formaldehyde, acetaldehyde, pentanal, hexanal, and nonanal, known products of indoor ozone chemistry, showed fairly large positive correlations with ambient ozone. The association between ambient ozone and nonanal was particularly strong. All these compounds are known sensory irritants with low odor thresholds. It is also likely that unmeasured irritating co-reaction products contributed to the reported BRS.

Conclusions

A clear relationship between ambient ozone concentrations and building-related health symptoms was identified in this study. The hypothesis that the cause of these symptoms is ozone-initiated indoor chemistry is supported by the positive correlation between ozone and aldehydes. Caution must be taken not to place too much credence on this single study, and replication is needed to verify the findings. If additional studies support these findings, the implication is that reduction of ambient ozone entrained into building HVAC systems before it can react with indoor air and surfaces has the potential to significantly reduce BRS.

Acknowledgements

This article was supported by Grant Number 5 RO1 OH008117-02 from CDC–NIOSH. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC–NIOSH. This work was also supported by the Assistant Secretary for Energy Efficiency and Renewable Energy, Building Technologies under the Department of Energy Contract No. DE-AC02-05CH11231. We would like to thank Charles J. Weschler, Hal Levin and William J. Fisk for their input and suggestions on this manuscript. We would also like to extend thanks to John Girman and Greg Brunner of the US EPA for their input, and the US EPA for providing the data used in these analyses. Additional thanks go to Quanhong Lei-Gomez for her expert contributions to the SAS programming used in these analyses.

References

Apte, M. G. and Erdmann, C. A. (2002) Associations of indoor carbon dioxide concentrations, VOCs, environmental susceptibilities with mucous membrane and lower respiratory sick building syndrome symptoms in the BASE study: analyses of the 100 building dataset, Lawrence Berkeley National Laboratory Report LBNL-51570, Berkeley, CA.

Apte, M. G., Fisk, W. J. and Daisey, J. M. (2000) Associations between indoor CO2 concentrations and sick building syndrome symptoms in U.S. office buildings: an analysis of the 1994-1996 BASE study data, *Indoor Air*, **10**, 246.

Beko, G., Halas, O., Clausen, G. and Weschler, C. J. (2006) Initial studies of oxidation processes on filter surfaces and their impact on perceived air quality, *Indoor Air*, **16**, 56–64.

Bell, M. L., Peng, R. D. and Dominici, F. (2006) The exposure-response curve for ozone and risk of mortality and the adequacy of current ozone regulations, *Environ. Health Perspect.*, **114**, 532–536.

Buchanan, I.S.H., Mendell, M.J., Mirer, A. and Apte, M.G. (2008) Air Filter Materials, Outdoor Ozone and Building-related Symptoms in the BASE study, *Indoor Air*, **18**, 144–155.

Dalton, P. (2003) Upper airway irritation, odor perception and health risk due to airborne chemicals, *Toxicol. Lett.*, **140-141**, 239–248.

Destaillats, H., Lunden, M. M., Singer, B. C., Coleman, B. K., Hodgson, A. T., Weschler, C. J. and Nazaroff, W. W. (2006) Indoor secondary pollutants from household product emissions in the presence of ozone: a bench-scale chamber study, *Environ. Sci. Technol.*, **40**, 4421–4428.

EPA (2003) *A Standardized EPA Protocol for Characterizing Indoor Air Quality in Large Office Buildings*, Washington, DC, Office of Research and Development and Office of Air and Radiation, U.S. EPA.

Erdmann, C. A. and Apte, M. G. (2004) Mucous membrane and lower respiratory building related symptoms in relation to indoor carbon dioxide concentrations in the 100-building BASE dataset, *Indoor Air*, **14** (Suppl 8), 127–134.

Gendreau, M., Hufford, M. and Stone, A. (2003) Measuring clinical pain in chronic widespread pain: selected methodological issues, *Best Pract. Res. Clin. Rheumatol.*, **17**, 575–592.

Gundel, L. A., Sullivan, D. P., Katsapov, G. Y. and Fisk, W. J. (2002) *A Pilot Study of*

Energy Efficient Air Cleaning for Ozone, Berkeley, CA, Lawrence Berkeley Laboratory National Laboratory, LBNL-51836.

Hodgson, M. (2002) Indoor environmental exposure and symptoms, *Environ. Health Perspect.*, **110**(Suppl), 663–667.

Höppe, P., Peters, A., Rabe, G., Lindner, J., Jacobi, G., Fruhmann, G. and Nowak, D. (2003) Environmental ozone effects in different population subgroups, *Int. J. Hyg. Environ. Health*, **206**, 505–516.

Kelly, T. J. and Kinkead, D. A. (1993) Testing of chemically treated adsorbent air purifiers, *ASHRAE J.*, **35**, 14–23.

Kleinbaum, D. G., Kupper, L. L. and Morgenstern, H. (1982) *Epidemiologic Research: Principles and Quantitative Methods*, Belmont, CA, Lifetime Learning Publications.

Klenø, J. and Wolkoff, P. (2004) Changes in eye blink frequency as a measure of trigeminal stimulation by exposure to limonene oxidation products, isoprene oxidation products, and nitrate radicals, *Int. Arch. Occup. Environ. Health*, **77**, 235–243.

Knudsen, H. N., Nielsen, P. A., Clausen, P. A., Wilkins, C. K. and Wolkoff, P. (2003) Sensory evaluation of emissions from selected building products exposed to ozone, *Indoor Air*, **13**, 223–231.

Lee, K., Vallarino, J., Dumyahn, T., Özkaynak, H. and Spengler, J. D. (1999) Ozone decay rates in residences, *J. Air Waste Manage. Assoc.*, **49**, 1238–1244.

Levin, H. (1989) Sick building syndrome: review and exploration of causation hypotheses and control methods, IAQ89 The Human Equation: Health and Comfort, Proceedings of the ASHRAE/SOEH Conference IAQ, San Diego, CA, 263–274.

Levin, H. (1991) Critical building design factors for indoor air quality and climate: current status and predicted trends, *Indoor Air*, **1**, 79–92.

Lippmann, M. (1989) Effects of ozone on respiratory function and structure, *Annu. Rev. Public Health*, **10**, 49–67.

Mendell, M. J., Cozen, M., Lei-Gomez, Q., Brightman, H. S., Erdmann, C. A., Girman, J. R. and Womble, S. E. (2006) Indicators of moisture and ventilation system contamination in U.S. office buildings as risk factors for respiratory and mucous membrane symptoms: analyses of the EPA BASE data, *J. Occup. Environ. Hyg.*, **3**, 225–233.

Mølhave, L., Kjaergaard, S. K., Sigsgaard, T. and Lebowitz, M. (2005) Interaction between ozone and airborne particulate matter in office air, *Indoor Air*, **15**, 383–392.

Morrison, G. C., Nazaroff, W. W., Cano-Ruiz, J. A., Hodgson, A. T. and Modera, M. P. (1998) Indoor air quality impacts of ventilation ducts: ozone removal and emissions of volatile organic compounds, *J. Air Waste Manage. Assoc.*, **48**, 941–952.

Nazaroff, W. W., Coleman, B. K., Destaillats, H., Hodgson, A., Liu, T. D. L., Lunden, M. M., Singer, B. C. and Weschler, C. J. (2006) Indoor air chemistry: cleaning agents, ozone and toxic air contaminants, ARB Contract No. 01-336, Sacramento, CA, California Air Resources Board and the California Environmental Protection Agency: California Air Resources Board.

Nøjgaard, J. K., Christensen, K. B. and Wolkoff, P. (2005) The effect on human eye blink frequency by exposure to limonene oxidation products and methacrolein, *Toxicol. Lett.*, **156**, 241–251.

Nøjgaard, J. K., Nørgaard, A. W. and Wolkoff, P. (2007) On-line analysis of secondary ozonides from cyclohexene and d-limonene ozonolysis using atmospheric sampling townsend discharge ionization mass spectrometry, *Atmos. Environ.*, **41**, 8345–8354.

SAS. (1989) *SAS/STAT User*'s Guide, Version 6, 4th ed. Cary, NC, SAS Institute.

Selvin, S. (1995) *Practical Biostatistical Methods*, Belmont CA, Duxbury Press.

Seppänen, O. A., Fisk, W. J. and Mendell, M. J. (1999) Association of ventilation rates and CO2 concentrations with health and other responses in commercial and institutional buildings, *Indoor Air*, **9**, 226–252.

Shair, F. H. (1981) Relating indoor pollutant concentrations of ozone and sulfur dioxide to those outside: economic reduction of indoor ozone through selective filtration of the make-up air, *ASHRAE Trans.*, **87** (Part I), 116–139.

Shields, H., Weschler, C. J. and Naik, D. V. (1999) Ozone removal by charcoal filters after continuous extensive use (5 to 8 years). In: Raw, G., Aizlewood, C. and Warren, P. (eds) *Proceedings of Indoor Air 99*, vol. 4, London, Construction Research Communications, 49–54.

Subramanian, P., Reynolds, S., Breuer, G. and Whitten, P. (2000) Analysis of limonene as an indicator for the assessment of environmental air-quality and health symptoms in office buildings, *J. Environ. Sci. Health Part A: Toxic/Hazard. Subst. Environ. Eng.*, **35**, 999–1019.

Tamás, G., Weschler, C. J., Toftum, J. and Fanger, P. O. (2006) Influence of ozone-limonene reactions on perceived air quality, *Indoor Air*, **16**, 168–178.

TenBrinke, J., Selvin, S., Hodgson, A.T., Fisk, W.J., Mendell, M.J., Koshland, C.P. and Daisey, J.M. (1998) Development of New Volatile Organic Compound (VOC) Exposure Metrics and their Relationship to Sick Building Syndrome Symptoms, *Indoor Air*, **8**, 140–152.

Uhde, E. and Salthammer, T. (2007) Impact of reaction products from building materials and furnishings on indoor air quality – a review of recent advances in indoor chemistry, *Atmos. Environ.*, **41**, 3111–3128.

USEPA. (2007) *AIRS Database*, Washington, DC, United States Environmental Protection Agency, http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm

Weschler, C. J. (2000) Ozone in indoor environments: concentration and chemistry, *Indoor Air*, **10**, 269.

Weschler, C. J. (2004) Chemical reactions among indoor pollutants: what we've learned in the new millennium, *Indoor Air*, **14**, 184.

Weschler, C. J. (2006) Ozone's impact on public health: contributions from indoor exposures to ozone and products of ozone-initiated chemistry, *Environ. Health Perspect.*, **114**, 1489–1496.

Weschler, C. J., Hodgson, A. T. and Wooley, J. D. (1992) Indoor chemistry: ozone, volatile organic compounds, and carpets, *Environ. Sci. Technol.*, **26**, 2371–2377.

Weschler, C. J. and Shields, H. C. (1987) A detailed study of the effects of ventilation, filtration and outdoor air on the composition of indoor air at a telephone office building. In: Seifert, B., Esdorn, H., Fischer, M., Ruden, H. and Wegner, J. (eds) *Proceedings of Indoor Air* '87, Berlin, Institute for Water, Soil and Air Hygiene, **3**, 142–146.

Weschler, C. J. and Shields, H. C. (1994) Indoor chemistry involving O_3, NO, and NO2 as evidenced by 14 months of measurements at a site in southern California, *Environ. Sci. Technol.*, **28**, 2120–2132.

Weschler, C. J. and Shields, H. C. (2000) The influence of ventilation on reactions among indoor pollutants: modeling and experimental observations, *Indoor Air*, **10**, 92–100.

Weschler, C.J., Shields, H.C. and Naik, D.V. (1994) Ozone removal efficiencies of activated carbon filters after more than three years of continuous service, *ASHRAE Transactions*, **1**, 1121–1129.

Weschler, C. J., Wells, J. R., Poppendieck, D., Hubbard, H. and Pearce, T. A. (2006) Workgroup report: indoor chemistry and health, *Environ. Health Perspect.*, **114**, 442–446.

Wilkins, C. K., Clausen, P. A., Wolkoff, P., Larsen, S. T., Hammer, M., Larsen, K., Hansen, V. and Nielsen, G. D. (2001) Formation of strong airway irritants in mixtures of isoprene/ozone and isoprene/ozone/nitrogen dioxide, *Environ. Health Perspect.*, **109**, 937–941.

Wolkoff, P., Clausen, P. A., Wilkins, C. K. and Nielsen, G. D. (2000) Formation of strong airway irritants in terpene/ozone mixtures, *Indoor Air*, **10**, 82–91.

Wolkoff, P., Wilkins, C. K., Clausen, P. A. and Nielsen, G. D. (2006) Organic compounds in office environments – sensory

irritation, odor, measurements and the role of reactive chemistry, *Indoor Air*, **16**, 7–19.

Womble, S. E., Axelrad, R., Girman, J. R., Thompson, R. and Highsmith, V. R. (1993) EPA BASE program – collection baseline information on indoor air quality, *Proceedings of Indoor Air* '93, Helsinki, Finland, 821–825.

Womble, S. E., Ronca, E. L., Girman, J. R. and Brightman, H. S. (1996) Developing baseline information on buildings and indoor air quality (Base 95). In: Teichman, K.Y. (ed.) *Proceedings of IAQ 96/ Paths to Better Building Environments/ Health Symptoms in Building Occupants*, Baltimore, MD, ASHRAE Conference IAQ 96, 109–117.

Zhao, P., Siegel, J. A. and Corsi, R. L. (2007) Ozone removal by HVAC filters, *Atmos. Environ.*, **41**, 3151–3160.