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EVALUATION OF HEALTH EFFECTS OF TOXIC AIR POLLUTANTS IN A SOUTHERN CALIFORNIA COMMUNITY: A PILOT STUDY

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ABSTRACT

Although acute adverse respiratory effects have been established for EPA criteria air pollutants such as ozone, there is little information on respiratory effects from air pollutants such as volatile organic compounds (VOCs) from outdoor toxic emission sources. We evaluated acute effects of air toxics in school children with asthma and characterized VOC exposures using subject time-activity reports, breath sample GC-MS, and personal, indoor home and outdoor stationary site VOC samplers. We recruited 26 Hispanics, ages 10-16, living in the Huntington Park, East Los Angeles County, an area flanked by major freeways and trucking routes. Subjects filled out symptom diaries and performed peak expiratory flow (PEF) lung maneuvers twice daily, Nov. 1999 to Jan. 2000. Two subjects dropped out, 4 had invalid diary/PEF data, and 1 had no breath samples. Central site measurements were made for VOCs and criteria air pollutant gases daily. On asthma episode and baseline symptom-free days, subjects collected samples of their exhaled breath in evacuated canisters; we analyzed these for 1,1-dichloroethane, benzene, carbon tetrachloride, chloroform, styrene, tetrachloroethylene, toluene, *m,p*-xylene, *o*-dichlorobenzene, *o*-xylene, and *p*-dichlorobenzene. Personal and indoor home VOC passive samples were collected in 4 subjects on 34 days. The ratios of breath VOC/indoor VOC were less than 1. Personal exposures were correlated with indoor exposures, but did not correlate with outdoor measurements for most VOCs. Only outdoor benzene, styrene and *m,p*-xylene on the previous two days appeared to be correlated with current day breath levels. Breath VOCs showed greater within- than between-individual variance. We found positive associations between asthma symptoms and breath concentrations of benzene (93 person-days), but not other VOCs. However, significant adverse effects of ambient VOCs on asthma symptoms (938 person-days) were found for benzene, 1,3-butadiene, ethylbenzene, styrene, tetrachloroethylene, toluene, *m,p*-xylene, *o*-xylene, acetone, acetaldehyde and formaldehyde. Symptoms were also positively associated with NO_2, SO_2 and O_3. In a subset of days with particle data available, symptoms were associated with organic and elemental carbon, which notably confounded effects of PM_{10}. Deficits in PEF in relation to pollutant increases were largely not statistically significant. This study has provided valuable insight regarding the measurement methods needed to assess personal VOC exposures and doses in children. Our findings are compatible with the view that many of these pollutants may be markers for a causal mixture of combustion-related pollutants in areas with high traffic density. Results suggest more work is needed on potentially causal air toxics in the pollutant mix from both traffic and industrial sources.

EXECUTIVE SUMMARY

Background: Acute adverse cardiorespiratory effects have been established for five of six principal criteria air pollutants (excluding lead) for which the US EPA has established so-called National Ambient Air Quality Standards. They include pollutant gases (ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide), particulate matter with aerodynamic diameters < 10 microns or PM_{10}), and fine particulate matter ($PM_{2.5}$). However, there is little epidemiologic information on the public health impact from air pollutants such as volatile organic compounds (VOCs) from outdoor toxic emission sources, which include automobiles and trucks. Therefore, there is a need to evaluate health effects of toxic air pollutants in communities near such emission sources. Complaints from the impacted communities of the South Coast Air Basin of California can be characterized as neurological (foul odors, headache, and nausea) or respiratory (breathing problems and asthma attacks). This project aimed to evaluate acute respiratory health effects of air toxics in a potentially susceptible population of asthmatic children living close to an air toxics monitoring site of the South Coast Air Quality Management District. An additional aim of the study was to characterize exposures to air toxics using subject reports of their time-activity patterns and a variety of approaches to measuring exposure to VOCs including chemical analysis of exhaled breath samples, and air samplers located on the person (personal exposure), indoors at the home, and at outdoor stationary regional sites. Results of this study will be useful in determining the type and scope of studies needed to evaluate exposures and acute health effects in California communities affected by multiple emission sources. This research relates to the Board's function in establishing air quality standards to protect human health. There have been no other studies to our knowledge conducted in California on the acute health effects of community exposures to VOCs or other airborne toxics in asthmatic children. The present study is the first epidemiologic study to evaluate the longitudinal relationship of acute asthma to exhaled breath measurements of VOC.

Methods: We recruited 26 Hispanic school children with asthma, ages 10-16, who lived in the Huntington Park area of East Los Angeles County, an area flanked by major freeways and trucking routes. Two dropped out and 4 had invalid diary or PEF data, leaving 20 subjects with 1,035 asthma symptom-days of observation over the period with outdoor pollution data (Nov. 4, 1999 through Jan. 23, 2000). Selected VOCs were measured in self-administered exhaled breath samples during a 3-month daily diary study (1 subject had no valid breath samples). Subjects were instructed to give breath samples during asthma flares and following baseline periods free of symptoms for three days. Ambient air pollutants were measured daily over the same period at centrally located stationary outdoor monitors. These pollutants included VOCs, criteria pollutant gases, and a subset of days with PM_{10}, organic and elemental carbon. Four volunteers were recruited from 24 participants in the panel for daily personal VOC exposure measurements and indoor home VOC exposure sampling over a 5-week period. They recorded in diaries their activities relevant to exposures. All subjects recorded health outcomes in paper diaries, and peak expiratory flow of the lungs using a non-electronic device twice daily. This allowed an analysis of health effects across all days in 20 subjects. Health effects were tested in longitudinal regression models controlling for temporal factors, weather and respiratory infections. Time series models predicting personal VOC exposure were estimated from the different exposure measurements and time-activity diary data for the 4 subjects.

Results: In the exposure assessment study we found the ratios of breath VOC/indoor VOC were less than 1. Personal exposures were correlated with indoor exposures, but did not correlate with outdoor measurements for most VOCs. Only outdoor benzene, styrene and *m,p*-xylene on the previous two days appeared to be correlated with current day breath levels, which showed greater within- than between-individual variance. Outdoor styrene and *m,p*-xylene of the previous day were associated with current day personal exposures. Time-activity diary data had limited predictive power. In the epidemiologic study, we found associations between bothersome or more severe asthma symptoms recorded in diaries and breath concentrations of benzene (93 person-days), particularly for episodes when asthma interfered with the daily activities of subjects. However, this last result was based on a small number of such asthma flares,

and other breath VOCs were nonsignificant. Analyses of ambient VOCs measured on the same person-days as breath VOCs showed notably stronger and significant associations with symptoms, including benzene, toluene, *m,p*-xylene and *o*-xylene. In the analysis of daily outdoor VOCs across the 3 months (up to 938 person-days) we found numerous positive associations of asthma symptoms with VOCs, NO_2, SO_2 and O_3. Significant effects of ambient VOCs on asthma symptoms were found for benzene, 1,3-butadiene, ethylbenzene, styrene, tetrachloroethylene, toluene, *m,p*-xylene, *o*-xylene, acetone, acetaldehyde and formaldehyde. A subset of days with particulate air pollution data showed associations between asthma symptoms and organic carbon, elemental carbon and PM_{10}. The strongest and most robust particle association was with organic carbon followed by elemental carbon, then PM_{10}. In two-pollutant models, PM_{10} did not confound the effects of organic and elemental carbon, but organic and elemental carbon confounded the effects of PM_{10}. Although deficits in peak expiratory flow of the lungs were found in relation to increases in some air pollutants, most findings were not statistically significant. We found limited evidence that the more severe asthmatics were at greater risk from pollutant exposures. The low frequency of asthma flares diminished our ability to assess effects of breath VOCs, and to assess pollutant effects on symptoms interfering with daily activities.

Conclusions: This pilot study has provided valuable insight regarding the measurement methods needed to assess personal exposures and doses in a potentially sensitive group of children. Our findings, coupled with experimental and other epidemiologic evidence in the literature, suggest that the pro-inflammatory and irritant nature of traffic-related pollutants can lead to adverse health effects in asthmatic children. Some VOCs measured in the present study, criteria air pollutants, organic and elemental carbon may be markers for a causal mixture of combustion-related pollutants in an area with high traffic density. Some limited evidence was found for adverse effects of process-related VOCs (styrene and tetrachloroethylene).

Recommendations for Further Study: Marked within-individual variability in breath sample measurements suggest that a longitudinal study with daily measurements is needed to further understand the temporal exposure-dose patterns of individuals. Our weaker results for breath versus ambient VOC exposures suggest the need for an improved study approach. It provides a compelling reason for a more extensive evaluation of: 1) other correlated air toxics exposures in ambient air such as organic compounds associated with particulate air pollutants, e.g., diesel exhaust particles; 2) personal exposures, including exposures of outdoor origin; and 3) advancement in the approach to using VOC breath samples in epidemiologic research (adding carbonyl compounds, measuring daily samples, adding exhaled markers of inflammation). Results suggest more work is needed on potentially causal air toxics in the pollutant mix from traffic and industrial sources. Our finding of positive association between acute adverse symptom outcomes in asthmatic children and ambient air toxics supports the need to evaluate both acute and chronic health effects in populations at risk. We strongly recommend the advancement of epidemiologic methods to investigate this important area of public health, including the measurement of personal exposure, use of electronic lung function meters and electronic diaries, and recruitment of children with persistent rather than intermittent asthma.

BODY OF REPORT

1. INTRODUCTION

1.1. Scope and Purpose of the Project

In summary, the present pilot health study and exposure assessment aimed to evaluate the acute adverse effects of air toxics in a potentially sensitive subpopulation of children living close to an air toxics monitoring site of the South Coast Air Quality Management District (SCAQMD). Subjects were school children with asthma living in the Huntington Park area of East Los Angeles County. The Huntington Park region of study was selected partly based upon results of the Multiple Air Toxics Exposure Study (MATES) II, which showed the area had the highest VOC level (SCAQMD, 2000). This region is flanked by 5 major freeways (5, 10, 60, 110, 710) and trucking routes. An additional aim of the study was to characterize exposures to air toxics using subject reports of their time-activity patterns and a variety of approaches to measuring exposure to VOCs including breath sample GC-MS, and personal, indoor home and outdoor stationary site samplers.

Specific Aim 1: We aimed to examine the relationship of the daily occurrence and severity of asthma among 24 asthmatic children to concentrations of volatile organic compounds (VOCs) measured in breath samples and at an outdoor stationary monitoring site. For this assessment, we tested exposure-response relationships in longitudinal regression models controlling for temporal factors, weather and respiratory infections (reported in daily diaries).

Selected VOCs were measured in exhaled breath air samples. These measurements have the potential to identify high-level exposures associated with residence near suspected point sources such as industrial plants (Wallace et al., 1991). Exhaled breath concentrations also have the potential to be markers of low-level VOC exposures in community settings as exemplified by studies on benzene exposure (Wallace, 1989).

We originally aimed to have subjects give breath samples during 4 asthma event days and 4 baseline symptom-free days. An asthma event was defined for subjects as asthma symptoms that required the use of as-needed medications, generally metered dose ß-agonist inhalers, as opposed to no event, in which case the breath sample was referred to as a "baseline" sample. The baseline attribute was instructed to subjects to mean no asthma symptoms that day or the previous two days. However, as described below, the severity of asthma was mild intermittent in the majority of subjects. Therefore, a minority of breath samples reflected asthma events reported in subject diaries that interfered with daily activities.

Ambient air pollutants were measured at a centrally located stationary outdoor monitoring site. These pollutants included: VOCs (including the compounds in breath measurements, plus carbonyl compounds), total elemental and organic compounds (EC-OC), and EPA criteria air pollutants (PM_{10}, O_3, NO_2, CO and SO_2). Several air pollutants that were planned to be sampled by the SCAQMD were not, including total polycyclic aromatic hydrocarbons and daily fine particulate air pollution. The other particle measurements that were planned to be sampled daily, including PM_{10} and EC-OC, were performed on a limited number of days by the SCAQMD.

Specific Aim 2: We also aimed to conduct an exposure assessment study to estimate the statistical associations between exhaled breath concentrations of VOCs from subjects described above and VOC concentrations measured at the outdoor stationary site. In addition, a subset of 4 subjects were selected from the 24 subjects for daily personal and indoor home exposure measurements. All exposure levels were compared. The exposure assessment aim followed the plan developed with faculty at the Research Triangle Institute (RTI), as follows:

a. to measure VOCs in the exhaled breath of 24 subjects at the onset of asthma exacerbations and at baseline asymptomatic days during a 12-week study period;
b. to conduct a 30-day follow-up of daily personal and indoor VOC exposures for a subset of 4 subjects using passive badges;
c. to investigate the relationships between personal exposures, indoor exposures, outdoor exposures, personal activity patterns, and other exposure sources by time-series analysis among the 4 subjects;
d. to investigate the relationships among breath VOC measurements, personal exposures, indoor home exposures, outdoor central site exposures, personal activity patterns, and other exposure sources among the 4 subjects and 24 subjects.

The results of this study are useful in determining the type and scope of studies needed to evaluate health impacts in California communities affected by multiple emission sources. This will guide the assessment of resources needed to fund various research designs, experimental and epidemiologic, to address environmental justice-related issues.

1.2. Review of the Literature on Childhood Asthma and VOCs

1.2.1. Overview: Asthma has been defined as having three phenotypic characteristics, as follows: 1) intermittent and reversible airway obstruction; 2) increased airway responsiveness to contractile stimuli; and 3) airway inflammation. Airways inflammation is a hallmark of asthma and is directly related to asthma severity as a function of acute and chronic airflow obstruction.

Epidemiological studies of asthma and ambient air pollution have primarily focused on five of six principal criteria air pollutants (excluding lead) for which the US EPA has established so-called National Ambient Air Quality Standards (NAAQS): O_3, particulate matter (PM), CO, NO_2, and SO_2. Studies in Europe have also used black smoke, which can represent sources of complex exposures such as diesel exhaust that have a high elemental carbon (EC) content. Acute asthma morbidity has been associated with these ambient air pollutants in both aggregate time series and individual-level repeated measures studies, as reviewed by Bascom et al. (1996). The causal components in the epidemiological studies have not been clearly identified, partly because the measurements have included only major criteria pollutants that: 1) co-vary with other unmeasured photochemically produced pollutants (e.g., O_3 with aldehydes); 2) involve mass concentrations of complex particle mixtures of unmeasured components that vary by space and time (e.g., black smoke, PM_{10} or $PM_{2.5}$); or 3) are correlated with other unmeasured co-generated primary pollutants (e.g., NO_2 or SO_2 with organic air toxics from fossil fuel combustion).

The lack of monitoring data and the regulatory focus partly explain the paucity of epidemiological data concerning other exposures such as air toxics. Experimental research on the respiratory effects of air toxics is largely limited to animal models or *in vitro* studies. This is not surprising given that many air toxics have potentially serious adverse consequences such as carcinogenic, reproductive or neurological effects.

Air toxics can be defined as having three characteristics, as follows: 1) they have the potential to cause serious adverse health effects in the general population or to organisms in the environment as a result of airborne exposures; 2) they are released from anthropogenic sources; and 3) they include 189 hazardous air pollutants listed in section 112.b.1 of the Clean Air Act. The primary focus of the present research is on a specific set of air toxics that are VOCs.

Some VOCs may be involved in inflammatory processes in asthma through irritant-induced airway injury. Chemical irritants may also act as neuronal triggers of so-called neurogenic inflammation (American Thoracic Society, 1999; Meggs, 1993). This could occur through irritant-induced induction of inflammatory mediators that trigger nonadrenergic, noncholinergic nerves to release tachykinins. Tachykinins are involved in regulation of bronchomotor tone and mucus secretion, and induction of plasma protein extravasation from increased postcapillary venular permeability (Maggi et al., 1995). This process may serve to enhance ongoing inflammation in the asthmatic lung caused by known immune triggers such as high molecular weight allergens. A cascade of bronchoconstrictive reflexes and of inflammatory events can follow. Examples consistent with this hypothetical mechanism include the putative interaction between irritant effects of ozone and pollen allergens in asthma exacerbations (Molfino et al., 1991), and the finding in subjects with mild asthma that airway responsiveness to inhaled allergen increases after ozone challenge (Jörres et al., 1996). Airborne irritants could also indirectly enhance neuroinflammation by inhibition of neutral endopeptidase (NEP). NEP degrades tachykinins and its levels are decreased following exposure to oxidants (Koto et al., 1995), cigarette smoke (Dusser et al, 1989) and an agent responsible for a form of occupational asthma, toluene diisocyanate (TDI) (Sheppard et al., 1988).

Some VOCs are believed to act as haptens that are involved in IgE-mediated reactions, which are key in early-phase asthmatic reactions (within minutes). Haptens must first react with endogenous or exogenous proteins to form a complete antigen. Formaldehyde is an important example of a VOC that likely functions in this manner. It combines with albumen to induce allergic sensitization to the hapten. Formaldehyde occurs in ambient air primarily as a result of automobile and diesel exhaust emissions. However, most epidemiologic studies have focused on effects of formaldehyde in indoor air from indoor sources such as pressed particleboard and paint.

1.2.2. Formaldehyde, asthma and atopy in children: Workplace exposure to formaldehyde has been linked to the onset of occupational asthma (Bernstein et al., 1999). The relationship of asthma and atopy in children to formaldehyde in several epidemiologic studies serves to exemplify one of the few VOCs also associated with asthma in the non-occupational literature. Therefore, formaldehyde is an air toxic that may have acute adverse health effects from low (non-occupational) to high (occupational) exposure levels. However, there is little available non-occupational data on the risk of asthma onset from formaldehyde.

One study passively measured formaldehyde over two weeks in the homes of 298 children and 613 adults (Krzyzanowski et al., 1990). In log-linear models controlling for SES variables and ethnicity, the study found a significantly higher prevalence of physician-diagnosed asthma and chronic bronchitis in children ages 6-15 years living in homes with higher formaldehyde concentrations over 41 ppb (6 asthma and 6 bronchitis cases). However, the room-specific measurements revealed that the association was attributable to high formaldehyde concentrations (> 60 ppb) in kitchens, particularly those homes with ETS exposures (5 asthma cases, 5 bronchitis cases), suggesting possible confounding by other factors not measured. In random effects models controlling for SES and ETS they found significant inverse associations between morning PEF rates and average formaldehyde from the bedroom, and between evening PEF and household average formaldehyde. There was no apparent threshold level. The PEF finding was independent of ETS, but the effects of age or of anthropomorphic factors was not mentioned. Symptoms of chronic cough and wheeze were higher, and PEF lower, in adults living in houses with higher formaldehyde levels. There was a significant interaction between formaldehyde and tobacco smoking in relation to cough in adults. Passive measurements of NO_2 did not confound the formaldehyde associations in children or adults.

Other non-occupational data on formaldehyde relates indirectly to asthma. Wantke et al. (1996) evaluated levels of specific IgE to formaldehyde using RAST in 62 eight-year-old children attending (for 2.5 years) one school with particleboard paneling and urea foam window framing. The children were transferred to a brick building (23-29 ppb formaldehyde) because of elevated formaldehyde levels in particleboard classrooms (43-75 ppb) and complaints of headache, cough, rhinitis and nosebleeds. Symptoms and specific IgE were examined before and 3 months after cessation of exposure. At baseline, three children had RAST classes ≥2 (positive) and 21 had classes ≥1.3 (elevated), while all 19 control children attending another school all had classes <1.3. After transfer, the RAST classes significantly decreased from 1.7 ± 0.5 to 1.2 ± 0.2 ($p < 0.002$) and symptoms decreased. However, IgE levels did not correlate with symptoms. None of the children had asthma.

Garrett et al. (1999) hypothesized that formaldehyde may adversely affect the lower respiratory tract by increasing the risk of allergic sensitization to common allergens. They studied 43 homes with at least one asthmatic child (53 asthmatic, 30 non-asthmatic) and 37 homes with only non-asthmatic children (N = 65). Atopy was evaluated in the children (aged 7-14) with skin prick tests (SPT) for allergy to 12 common animal, fungal and pollen allergens. Formaldehyde was measured passively throughout the homes over 4 days in 4 different times of 1 year. Atopic sensitization by SPT was associated with formaldehyde levels (OR for 20 $\mu g/m^3$ increase, 1.42, 95% CI, 0.99-2.04). Across three formaldehyde exposure categories, there was also a significant increase in the number of positive SPTs, and in the wheal ratio of allergen SPT over histamine SPT. Mean respiratory symptom scores were significantly and positively associated across the three categories. There was a significant positive association between parent reported physician-diagnosed asthma and formaldehyde, but this was confounded by history of parental asthma and parental allergy. However, it is unclear why these familial determinants were treated as confounders rather than effect modifiers, although knowledge of asthma by parents may lead to bias in the assessment of asthma in their children.

Several other studies of non-asthmatic subjects have examined health outcomes and biomarkers that are relevant to asthma. Franklin et al. (2000) studied 224 children ages 6-13 with no history of upper or lower respiratory tract diseases. They used expired nitric oxide (eNO) as a marker for lower airway inflammation (Barnes, 1995). Formaldehyde was passively monitored in the children's homes for 3-4 days. Maximum end expiratory eNO was measured in each child with a fast response chemiluminescence analyzer. They found no association of formaldehyde with lung function. However, controlling for age and atopy (by SPT), eNO was significantly elevated to 15.5 ppb (95% CI, 10.5, 22.9) in homes with ≥ 50 ppb formaldehyde as compared with 8.7 ppb eNO (95% CI, 7.9, 9.6) in homes with < 50 ppb formaldehyde. Authors did not report the risk of atopy to common allergens from exposure to formaldehyde. They hypothesized that formaldehyde causes inflammation and the release of cytokines, which leads to the upregulation of inducible NO synthetase. This view was supported by another study that found intranasal exposure to 400 ppb formaldehyde in healthy subjects caused eosinophilia in the nasal epithelium (Pazdrak et al., 1993).

1.2.3. Experimental evidence for VOC mixtures: Indirect evidence of a role for ambient VOCs in asthma comes from research linking a buildup of indoor irritants including VOCs and bioaerosols in office buildings to a nonspecific cluster of symptoms called the "sick building syndrome," which includes upper and lower respiratory tract symptoms, eye irritation, headache and fatigue. Other studies have also found new onset asthma occurring in relation to particular nonresidential indoor environments, especially where problems with ventilation systems or dampness have been found (IOM, 2000). It is possible that fungal spores or other aeroallergens, mycotoxins and endotoxins could increase in parallel with VOCs under conditions of inadequate air exchange at work, and be responsible for some of these findings.

Some experimental evidence in controlled human exposure studies supports an irritant mechanism for VOCs (Molhave et al., 1986, Koren et al., 1992), but the human experimental research on lower respiratory or pulmonary immunological effects of VOCs is scarce apart from studies of agents associated with occupational asthma (e.g., TDI, formaldehyde).

Koren et al. (1992) conducted a randomized crossover chamber study of 14 healthy nonsmoking young adult men. Subjects were exposed for 4 h, 1-wk. apart to clean air, and 25 mg/m^3 of a VOC mixture typical of indoor non-industrial microenvironments. Nasal lavage performed immediately after exposure and 18 h later, showed significant increases in neutrophils at both time points. Harving et al. (1991) conducted a randomized crossover chamber study of 11 mild asthmatics who were hyperreactivity to histamine. Subjects were exposed for 90 min, one week apart to clean air, and VOC mixtures at 2.5 and 25 mg/m^3. Investigators found forced expiratory volume in 1 second (FEV_1) decreased to 91% of baseline with 25 mg/m^3, but this was not significantly different from sham exposure and there was no change in histamine reactivity. It is possible that the null results do not reflect inflammatory changes that influence small airways, which could be missed with FEV_1 measurements. What may be occurring in natural environments is another story, with mixed exposures possibly interacting under a wide range of exposure-dose conditions. This is best investigated with epidemiological designs.

1.2.4. Epidemiological evidence for VOC mixtures: Epidemiologic evidence linking indoor home VOCs with asthma or related respiratory outcomes come largely from cross-sectional studies. A survey of 627 students ages 13-14 yr attending 11 schools in Uppsala, Sweden, showed self-reported asthma prevalence (N=40) was higher in schools with higher VOCs (Smedje et al., 1997). Other risk factors (e.g., aeroallergens) were not controlled for in this association. Also, passive, not active, VOC measurements were associated with asthma.

Norbäck et al. (1995), using a survey sample of 600 adults ages 20-44 yr in Uppsala, Sweden, selected a nonrandom subsample of 47 subjects either reporting asthma attacks or nocturnal breathlessness the last 12 months or reporting current use of asthma medications. A random subsample of 41 other subjects was selected from the survey pool with negative responses. Logistic regression models adjusted for age, sex, smoking, carpeting, and house dust mites, but did not adjust for dampness, which was significant. There were no associations of daytime breathlessness with concentrations of 2-hr active VOC samples in the homes. Nocturnal breathlessness was associated with toluene, C8-aromatics, terpenes and formaldehyde in adjusted models. Bronchial hyperresponsiveness was only correlated with limonene. PEF variability was only correlated with terpenes.

Wieslander et al. (1997) aimed to examine respiratory symptoms and asthma outcomes in relation to indoor paint exposures in the last year. They selected an random sample of 562 adult subjects, including asymptomatic responders along with an enriched sample of all reporting asthma or nocturnal dyspnea (216 subjects), using the same survey source population living in Uppsala as Norbäck et al. (1995). Asthma was defined as positive bronchial hyperresponsiveness to methacholine plus asthma symptoms (99 subjects). Thirty-two percent of homes and 23 percent of workplaces were painted within the last year. Total VOC was elevated by 100 μg/m^3 in 62 newly painted homes. Logistic regression models only adjusted for age, sex and current smoking, but not ETS. Blood eosinophil concentrations and asthma prevalence was greater for homes with newly painted kitchens or woodwork (OR 1.5, 95% CI 1.0-2.4), consistent with greater differences in VOCs (especially 2,2,4-trimethyl 1,3-pentanediol diisobutyrate and formaldehyde). In newly painted workplaces, asthma-like symptoms were significantly increased (wheeze, dyspnea), but there was no association with bronchial hyperresponsiveness or eosinophils. There were no associations for newly painted homes or workplaces and atopy (SPT), serum eosinophilic cationic protein, serum IgE, PEF variability (1 week self-administered twice/d), or in-clinic FEV_1. Biases

in the two cross-sectional studies in Uppsala, Sweden, above include potential selection bias and the possibility that health outcomes preceded exposures.

Diez et al. (2000) studied 266 newborn children in Leipzig, Germany, either born with birth weight of 1500-2500 g, or with elevated IgE in cord blood, or with a positive primary family history of atopic disease. Concentrations of 25 VOCs were monitored indoors during the first 4 weeks of life. Parents filled out questionnaires after 6 weeks and 1 year of age. Postnatal respiratory infections were associated with benzene > 5.6 $\mu g/m^3$ (OR 2.4, 95% CI 1.3, 4.5) and styrene > 2.0 $\mu g/m^3$ (OR 2.1, 95% CI 1.1, 4.2). Wheezing was associated with reports of restoration (including painting and installation of carpeting) during the first year of life, but not with total or specific IgE at the age of 1 year. These models controlled for heating, gas cooking, home size, new furniture and pets, but did not control for significant associations with ETS, which was correlated with benzene.

All of the above studies of indoor VOCs may be subject to unmeasured confounding by other causal agents that increase indoors under low ventilation conditions or increase for other reasons (e.g., aeroallergens with dampness). Most, but not all, of the studies controlled for ETS. In summary, the research to date is too sparse to evaluate causality from indoor home VOCs, but there is even less information to evaluate the public health impact on respiratory health from outdoor ambient VOCs, which include some of the same compounds found indoors.

Ware et al. (1993) conducted a study of ambient VOCs in a large chemical manufacturing center in the Kanawha Valley, WV. They surveyed 74 elementary schools with interviews of 8,549 children in and out of the valley and measured passive 8-wk samples of 5 petroleum-related VOCs (toluene, *m,p*-xylene, benzene, *o*-xylene, decane) and 10 process-related VOCs (1,1,1,-trichloroethane, carbon tetrachloride, 1-butanol, chloroform, perchloroethylene, methyl isobutyl ketone, 1,2-dichloroethane, styrene, mesityl oxide, 2-ethoxyethyl acetate). Higher VOC concentrations were found in the valley. Cross-sectional results showed children in the valley had higher rates of physician-diagnosed asthma: OR 1.27 (95% CI 1.09, 1.48). Composite indicators for lower respiratory symptoms in the last year were weakly positively associated with petroleum-related VOC levels (OR per 10 $\mu g/m^3$, 1.05, 95% CI 1.02, 1.07) and process-related VOCs levels (OR per 2 $\mu g/m^3$, 1.08, 95% CI 1.02, 1.14). Asthma diagnoses were weakly positively associated with petroleum-related VOCs (OR 1.05, 95% CI 1.02, 1.08), but not process-related VOCs (OR 0.99). One school with high petroleum-related VOCs strongly influenced the model.

The average concentrations measured in the Kanawha study do not differ greatly from average levels in large urban areas (Leikauf et al, 1995). For the Kanawha study compared with a Los Angeles exposure study, for example, average toluene was 9.7 $\mu g/m^3$ vs. 13 $\mu g/m^3$, respectively, and for benzene, 3.2 $\mu g/m^3$ vs. 3.5 $\mu g/m^3$, respectively (SCAQMD, 2000). In a study of 51 residents of Los Angeles, CA, personal and indoor air concentrations of all prevalent VOCs except carbon tetrachloride were higher than outdoor concentrations (Wallace et al., 1991). Also, personal real-time exposures can be even higher, particularly while in cars (Wixtrom et al., 1992). For example, measurements of toluene taken inside cars in New York City ranged from 26 to 56 $\mu g/m^3$, and for benzene ranged from 9 to 11 $\mu g/m^3$ (Weisel et al., 1992).

1.3. Exposure Assessment for Volatile Organic Compounds

Several researchers have studied the relationships between personal, indoor, outdoor, and breath VOC concentrations (Wallace et al., 1991; Wallace et al., 1993; Wallace et al., 1997; Lioy et al., 1991). These studies have demonstrated breath measurements to be a precise and noninvasive method of determining body burden of VOCs. Integrated personal and individual samples normally need a 24-hour sampling period to achieve the desired detection limit. In comparison, a unique advantage of exhaled breath is that

it can provide snapshots of dose at a given time point. This advantage is important in investigating environmental factors that trigger the onset of acute disease conditions, such as asthma attacks.

2. MATERIALS AND METHODS

2.1. Epidemiologic Research Design

This is a panel study involving an investigation of the relationship of repeated measures of health outcomes (asthma symptoms and peak expiratory flow rate) and exposures in children with asthma (*Specific Aim 1*). Subjects lived and attended school in the Huntington Park region, Los Angeles County, California during the follow-up period with ambient exposure data of November 4, 1999 through January 23, 2000. This exposure period followed a 5-10 day run-in training period for each subject. Some breath canister samples were collected on Nov 1-3 as well. Health outcomes and outdoor air pollution were measured daily over the 3 months yielding a daily repeated time series. Breath VOCs were evaluated using GC-MS measurements of exhaled breath samples taken by subjects. Exposure-response relationships between for these breath VOC samples and health outcomes were compared to exposure-response relationships using outdoor ambient VOC data.

This longitudinal study approach provides information concerning the etiologic nature of acute asthma episodes not possible with other research designs using longer time resolutions. Korn and Whittemore (1979) originally adapted the panel design to study the daily effects of air pollutants on the probability of acute asthma attacks. The design makes it possible to determine the temporality of associations (i.e., to test whether the putative cause precedes the outcome), and to observe individual patterns of change in exposure and response (Weiss and Ware, 1996). These advantages are particularly well suited to the study of illnesses such as asthma with acute-on-chronic patterns of change. The study design is statistically efficient (enhanced signal-to-noise ratio) in a manner similar to a cross-over clinical trial design because: 1) multiple treatment or exposure conditions are studied in each subject**;** and 2) variability in exposure-response relationships due to between-subject characteristics is controlled for by the repeated measures characteristic of the design (Louis, 1984). The last advantage is due to a reduction in the variability of the response variable without reductions in the magnitude of the exposure-response relationship, thereby enhancing power and precision (Weiss and Ware, 1996). Other major advantages of the proposed design are that the use of daily diaries reduces the likelihood of recall bias given the proximity of events, and that each subject can serve as his or her own control over time.

2.2. Site and Time Period Selection

The region around Huntington Park was selected as the study site in consultation with CARB and SCAQMD personnel. We chose the site based on the historically high concentrations of VOCs as reported in the MATES II study (SCAQMD, 2000). The sources of VOC in the Huntington Park region are predominantly attributable to traffic density, trucking routes and air transport, with some additional contribution by local light industry. The site was also desirable because of its proximity to the Environmental Health Service of the Rancho Los Amigos National Rehabilitation Center (RLANRC). This was the subcontract site (directed by Dr. Henry Gong) charged with the recruitment and follow-up of study subjects. Also, the demographic characteristics were desirable given the high percentage of Hispanics (around 97%) and stable households. RLANRC had established communication linkages with school and city officials, which was further enhanced during the recruitment phase of the study.

In selection of the central outdoor monitoring site, the local MATES II site (Huntington Park Fire Station) was deemed to be no longer suitable because of physical restrictions. The SCAQMD, along with input from our group, selected an alternate site at the Nimitz Middle School. There was a delay in the start of

sampling by SCAQMD at the Nimitz site until Nov 19, 1999, due to electrical outlets (power company delays and power outages). This was not considered a sufficient reason to delay the start of the study because an alternate MATES II site was available and operational starting Nov 4, 1999. The alternate site was just adjacent to Huntington Park (Heliotrope Avenue Elementary School in the city of Maywood). The Heliotrope site was actually nearer to 8 out of 26 volunteers than the Nimitz site (map, Figure 4.1). Subjects were located within a 2.6-mile radius study area from the central Nimitz Middle School monitoring site, except one subject at 3.8 miles. Subjects lived in the incorporated cities of Huntington Park, Maywood, Bell, and South Gate, and the unincorporated Los Angeles community of Florence-Graham. However, for the purposes of this report, the area of study will be simply referred to as the Huntington Park region.

There was a SCAQMD staff holiday break in ambient VOC collection from Dec 31, 1999 through Jan 4, 2000. Collection of VOC canisters resumed from Jan. 5 through Jan. 23, 2000. In addition to VOCs, criteria air pollutant gases (O_3, NO_2, SO_2 and CO) were also collected at both sites. Data for criteria air pollutant gases was missing for first week, with collection beginning on Nov 11, 1999 and continuing daily through Jan. 23, 2000. At the Heliotrope site, 24-hr gravimetric PM_{10}, and elemental and organic carbon fractions were measured on Nov. 4 through 26, and on Dec 8 and 14. At the Nimitz site, PM_{10} was measured continuously with a tapered element oscillating microbalance (TEOM) from Dec. 19 through 28, 1999. Data for the TEOM $PM_{2.5}$ was not valid, with numerous negative values.

The study period was originally selected to be 8 weeks from November through December 1999, and later extended to January 23, 2000 to complete the proposed task of collecting 192 VOC breath samples (discussed below). These 3 months were reported have the highest monthly average concentrations for 1,3 butadiene (1.01-1.18 ppb) and benzene (2.03-2.35 ppb) during the MATES II monitoring period of June, 1998 to March, 1999 in Huntington Park (SCAQMD, 2000).

We decided that it was necessary to continue the study for an additional 4 weeks from Dec 27, 1999 to Jan. 24, 2000. The following reasons made this necessary:

1) The late arrival of funds from ARB resulted in a 1-week delay in the start of the VOC canister component of the study (Oct. 25 delayed to Nov. 1, leaving 7 weeks total) and exposure assessment component (Nov. 9 delayed to Nov. 16, leaving 5 weeks total) due to equipment and supply needs at RTI.
2) RTI's mass spectrometer (for VOC canisters) malfunctioned beginning in mid-November and continuing for over 2 weeks;
3) We achieved our target for initial recruitment of 27 subjects by recruiting less severe asthmatics than planned (see eligibility requirements, next section). Also, the reported historical asthma severity of several asthmatics overestimated their follow-up severity. By the end of the first week of December, 6 subjects had not had any asthma exacerbations with a score greater than 2 (asthma exacerbation interfering with daily activities). Another 6 had only provided 1 baseline VOC breath sample and 1 event VOC breath sample with a diary symptom score > 2. Only 14 subjects had given at least two event VOC breath samples given by the end of November. By the end of the 7-week follow-up period we had only 113 VOC breath samples, 79 short of the targeted number.

The more severely asthmatic subjects who were also compliant with study procedures (as determined by RLANRC field staff) were the subjects recruited for additional follow-up (total 11 subjects). Two of these subjects were among the 4 who were in the 34-day exposure assessment phase. After the additional 4 weeks of follow-up, the final number of VOC breath canisters was 146.

Aside from the need, there was a benefit to continuing the study. First, the additional 4 weeks of follow-up increased the sample size of diary entries for both the epidemiologic and exposure assessment components from 8 weeks to 12 weeks of daily data. In line with the pilot nature of this study, we have also gained considerable insight into designing approaches to recruitment and training for any future study in this or a similar community.

2.3. Recruitment and Eligibility Criteria

We aimed to follow a cohort of 24 pediatric subjects with daily symptom and time-activity diaries. Subjects were recruited from area schools using a school-based recruitment protocol. Recruitment instruments included a flyer (Appendix A). The flyer was available at volunteer school sites. A letter to school principals was sent out by Dr. Gong to inform them about the study and to gain their support for the project.

A screening questionnaire was used to assess eligibility (Appendix A). The following were the eligibility criteria for children with asthma:

1) age 10-15, to recruit children who are old enough to complete diaries, but too young to drive, or to work in occupations with potential VOC exposures;
2) nonsmokers who live in nonsmoking households;
3) home address and school address in the study area around the Nimitz Middle School central monitoring site (Figure 4.1: 2.6 mile radius);
4) physician-diagnosed asthma; a minimum 1 year history of asthma;
5) persistent severity of asthma as defined by the National Heart Lung and Blood Institute's Clinical Practice Guidelines (NHLBI, 1997) (at least 2 symptomatic days per week during the summer/fall seasons requiring as-needed β-agonist inhaler use to treat bothersome symptoms that may interfere with daily activities).

The first two criteria were intended to control for other major sources of exposure, namely, active and passive tobacco smoke, occupational exposures, and frequent and long exposures to vehicular travel. The criteria number 5 was not achieved after it became evident to the RLANRC team that the recruitment target of 24 subjects would not be met in time for the high VOC exposure season of late fall, early winter, 1999 unless subjects with more intermittent asthma were recruited. Also, two 16 year olds were recruited to obtain the recruitment target. These subjects did not have regular use of cars and did not have regular jobs.

Four subjects were recruited for an intensive personal exposure assessment project (see Section 2.11, Exposure Assessment Methods). They were selected from all volunteers who consented to participate in that phase of the study prior to the beginning of the panel follow-up. The four were selected using information on the following: 1) the level of compliance in first weeks of the panel; 2) the level of comprehension of study procedures (as assessed by the field team); and 3) an adequate frequency of asthma symptom episodes for an informative analysis of individual time series. The selected subjects (through their parents) were telephoned and invited to begin the intensive exposure assessment in week 3, Nov. 16 through Dec. 21, 1999 (for a total of 34 days or 136 personal and 136 indoor passive badge VOC samples).

We aimed to recruit subjects through public and private schools and physicians offices. Only recruitment through the schools was successful. Volunteer subjects were ages 10-16 and had physician-diagnosed asthma. Monetary incentive offered to subjects was thought to be a motivating factor. Having fluently bilingual field workers familiar with the study community, as well as support from several local school administrators and city officials helped the recruitment effort. Instruments, including consent forms and recruitment flyers were all translated into Spanish by RLANRC staff. Despite the fact that recruited

subjects were asked to wait for many weeks to months to begin the study because of delayed funding of the CARB portion, no dropouts resulted prior to the start of the study and only one dropout occurred during the study.

The target recruitment number was 27 to account for a 10% dropout rate in order to achieve a sample size of 24 subjects. RLANRC recruited 26 subjects, but only one dropped out (12 year old Hispanic male) after 5 weeks and 25 continued for 7 weeks. The reason given for the dropout was an extended out-of-town family trip. In the judgment of the field staff, this subject and parents' motivation was low, as evidenced by less-than-optimum breath sampling (1 baseline sample) and by poor diary recording (did not complete any time-activity diaries). Another subject (10 year old Hispanic male) did not properly complete the asthma diary despite repeated attempts at retraining. Therefore, 2 subjects were excluded from further study due to noncompliance leaving the total sample at 24 subjects for the epidemiologic analysis, which was the target sample size. The data for the two excluded subjects were not keypunched.

The institutional review boards of RLANRC and University of California, Irvine (UCI) approved the study protocol. Informed written consent in Spanish or English was obtained from all subjects and one of their legal guardians. Subjects and their parents were blinded to the substances being monitored. The breath samples were referred to as measurements of changes in the chemistry of the body, which is true. In addition, subjects and their parents were blinded to the monitoring of community air pollutants as a study exposure since they may be made aware of regional pollution episodes through alerts or other indicators. This could bias responses in some subjects. The study was referred to as an investigation of the determinants of asthma.

2.4. Baseline Assessment

The baseline Health Questionnaire developed for this study was a modification of the RLANRC Environmental Health Service questionnaire (Appendix B), which is, in part, derived from the questionnaire developed for the American Thoracic Societies' Epidemiology Standardization Projects (Ferris, 1978). Modifications were made mainly to the environmental inventory using questions from a similar questionnaire from UCI and input from RTI investigators. The asthma history section was expanded as well. An additional Environmental Inventory questionnaire was administered with questions provided by RTI to assist them in evaluating VOC sources (Appendix C). The baseline questionnaires and training session were interview-administered to each subject and one of their parents before the start of the panel follow-up.

A research assistant visited the home of each subject to administer the baseline questionnaires and training session with parents and subjects. The questionnaire included questions on:

1) demographics -- age, sex, race/ethnicity, education level, and income level (parents of children);
2) height and weight;
3) asthma history (e.g. age at onset, approximate number of times/yr. physicians or emergency rooms are visited for exacerbations, usual symptoms and their frequency);
4) currently prescribed medications;
5) history of medication use;
6) known or suspected symptom triggers;
7) other medical history;
8) passive/active smoking exposures;
9) exposure profile (e.g., hobbies, traffic density, pets, dust avoidance measures, proximity to busy streets and freeways);
10) indoor air pollutant point sources (building characteristics, renovation, carpeting, garage, heating and cooking energy source, proximity to busy streets, household products with VOCs, etc.);

11) family history of asthma and atopic diseases, and migraine;
12) to aid in identifying aeroallergen-related asthma, subjects were asked whether symptoms of asthma occur at the same time as symptoms of allergic rhinitis, particularly during certain months of the year.

2.5. Training

After the initial training session when the baseline questionnaires were administered, all subjects were familiarized a second time just before the start of the panel in the use of the VOC canister by the use of a training unit (see Exposure Assessment Methods). The daily diary procedures were also reviewed. A subject guide was developed in language that the children could understand (all spoke English) (Appendix D). Retraining was administered for subjects after the first week for diary and PEF procedures that appeared to be performed incorrectly.

2.6. Subject Tasks

2.6.1. Overview: For the panel follow-up, subjects were instructed to complete a short daily diary each evening that included questions on symptoms, medication use and potential risk factors for asthma. Subjects provided the following: 1) diary data on asthma symptoms, medication use and other relevant outcome data every day; 2) detailed time-activity diary (TAD) for time-place–activity profiles every 2 hours; 3) three peak expiratory flow (PEF) maneuvers in the morning and 3 in the evening; and 4) samples of exhaled breath, collected in evacuated 1.5 L Summa-type canisters during asthma events and after more than 2 days free of symptoms (baseline). Subjects and parents were instructed repeatedly to balance the number of event and baseline samples.

We also conducted a baseline and an end-of-study spirometry test session to aid in the assessment of asthma severity using percent predicted FEV_1.

2.6.2. Daily Asthma Diary: The participant reported the daily severity of asthma using an asthma symptom severity scale based, in part, upon impacts on quality of life. They also reported the number inhaler puffs from as-needed ß-agonist medications. The Children's Asthma Study Diary (Appendix E) was a modification of the diary used in previous NIH-funded studies for assessing asthma outcomes (NIH, NIEHS ES06214, PI, R. Delfino). Detailed descriptions of the symptom levels and illnesses (asthma, allergy, respiratory infections and headache) were included on the reverse side of the diary. A blank comment section was available for subjects to report problems.

Daily diary questions concerning asthma symptom severity emphasize the impact of the clinical severity of asthma on the normal daily activities that are typical for each individual. Subjects received training in interpreting the scoring system in this manner. Because the complex of symptoms recognized or experienced by asthmatics differs from one person to another, we have combined the rating of symptoms into one score that relates to the subject's quality of life.

Asthma symptoms (cough, wheeze, sputum production, shortness of breath and chest tightness) were rated by the subjects in terms of their combined severity on a scale from 0 to 5. This approach contrasts previous asthma panel studies that generally dichotomized each individual symptom into present or absent. The clinical severity of asthma in some asthmatics could be obscured by this approach.

Subjects classified the 6 levels of daily asthma severity as:
0 = no asthma symptoms present;
1 = asthma symptoms present, but caused no discomfort;
2 = asthma symptoms caused discomfort, but did not interfere with daily activities or sleep;
3 = asthma symptoms interfered somewhat with daily activities or sleep;
4 = asthma symptoms interfered with most activities, and may have required that the participants stay home in bed, return home early from school or work, or call a doctor or nurse for advice;
5 = asthma symptoms required either going to a hospital, emergency room or outpatient clinic.

Subjects also recorded in the diary the daily number of as-needed β-agonist inhaler puffs and other asthma medications prescribed for daily use for preventive maintenance (e.g., anti-inflammatory inhaled corticosteroids). This was used to assess the potential influence of anti-inflammatory medication use on estimates of pollutant effects as has been previously reported (Delfino, 1998).

2.6.3. Daily Peak expiratory flow rate (PEF): This is the maximum flow velocity (L/min) that can be generated during a forced expiratory maneuver starting with fully inflated lungs. Because it measures only large airway function, patients with mild asthma may have PEFs that appear normal despite small airways disease. Nevertheless, it provides a quantitative measure of large airway obstruction that can be obtained with inexpensive portable device. We used the Mini-Wright peak flow meter (Keller Medical Specialties Inc., Antioch, Illinois).

The subjects were instructed to take PEF measurements in the morning upon arising, and in the evening around 8 PM, always before the use of inhaled bronchodilators. All three maneuvers and time of the session were recorded by subjects in the Daily Asthma Diary. The highest of the 3 PEF maneuvers are retained for the analysis. Subjects were trained by staff and given written instructions (Appendices D and E).

2.7. Weekly Follow-up and Maintenance of Compliance

Subjects and at least one legal guardian were followed up weekly at their homes. This involved on-site validity checks to insure the accuracy of diaries and compliance with the study protocol. The used VOC canisters were also picked up at this time and new ones distributed. Parents and subjects had a chance to ask questions face-to-face with research staff. A final home follow-up occurred at the end of the monitoring period. Subjects who completed the panel study received certificates of appreciation.

Monetary incentives of $3 per day were used for each 2-weeks of completed follow-up to enhance continued participation and compliance with the study protocol ($6 per day for 4 subjects in the intensive exposure assessment), plus $3 for each breath VOC sample. Research staff were charged with maintaining the enthusiasm of subjects toward the overall study goal of asthma prevention through an understanding of causation. The incentives and weekly follow-up visits successfully maintained compliance as evidenced by the low dropout rate (<10%).

UCI staff modified a follow-up procedures guide for asthma panel studies for the use by RLANRC staff. A weekly follow-up validation checklist was provided for RLANRC staff to use when looking at the asthma diary responses collected at the weekly home site visit. These instruments are similar to those that have also been used in quality assurance and control (Flesh, 1981; Kraemer, 1989). Follow-up logs, phone logs and sample flow charts were developed by RLANRC for their use with input by UCI.

2.8. Instruments Translated into Spanish

The recruitment flyer, Health Questionnaire, peak flow instructions for the Subject Guide, and Children's Asthma Study Diary were translated into Spanish using words and phrasing commonly used in the target community. The Spanish translations were primarily for the use of parents of subjects, many of who were better able to comprehend the instructions in Spanish than in English.

2.9. Pilot Testing and Preparation for the Full Panel Study

RTI worked with RLANRC to pilot test the procedures for breath sample collection, indoor and personal sample collection, activity diary collection and exposure baseline questionnaire collection. Meetings between UCI and RLANRC with RTI on conference calls were conducted four times to advance these methods before deployment.

***2.9.1. Pilot Testing*:** A pilot test was conducted in Sep. 1999 to evaluate the procedures developed for field sample collection. RTI shipped all the necessary devices and accessories and examined the appropriateness of the procedures. The aspects examined included the following:

a. *Breath collection procedures* - Fourteen canisters were collected in the pilot test. The pressure of each canister was measured. The results indicated that the subjects were able to correctly follow breath sample collection procedures.
b. *Color-coding system of the indoor and personal badges* - A subject was followed for a week using a color-coding system to change the badges. The result indicated that the subject was able to correctly follow the procedures.
c. *TAD cards* were tested in 6 subjects. In general, the subjects were able to use the diary cards correctly. Some confusion was found in the recording and we revised our instructions accordingly.
d. *Baseline health and exposure questionnaires* – no problems found.

The investigators decided to not deploy the Palm Pilot electronic diaries as originally proposed. This was based on two reasons: 1) development of a Palm diary program requires several months of testing and programming; 2) the late arrival of funds from CARB left insufficient time for RTI and UCI to develop and test a new Palm program. We have instead used the standard paper diary approach for this study.

In collaboration with UCI and RLANRC investigators, the RTI team achieved the following tasks in the development of instruments for the exposure assessment part of the project (Fully Discussed in Exposure Assessment Section *2.11.4.2*): preparation of breath sample collection devices, indoor and personal badges, analytical instruments, field quality control samples, portable diary cards for the TAD, a baseline environmental exposure questionnaire, and accessories for field sample collection.

In addition, RTI worked with RLANRC to prepare field sample collection protocols, including:

a. Instructions for using breath sample collection unit;
b. Instructions for using color coding system to collect indoor and personal badge samples;
c. Instructions for using diary cards;

RTI developed an information shell to keep track of the field samples, questionnaires and dairies. Data entry screens were programmed for entering TAD data (see Exposure Assessment Methods).

2.9.2. Investigation of possible interference of propellant (Freons) used in inhalers: RTI performed an evaluation of potential interference by the propellant (Freons) used in inhalants for asthma treatment in the analysis of VOCs in breath. The propellant in inhalers is usually chlorofluorocarbons (CFCs), which have, at least for the time being, been waived of legal requirements for phasing out the use of CFCs.

Breath samples were collected from a volunteer at RTI (smoker) who routinely uses an inhalant to treat his asthma condition. The subject normally uses the inhaler twice per day, two puffs in the evening and two puffs in the morning. A breath sample was collected before the morning dose (pre-dose), and then at 1, 5 and 15 minutes post dosage. Breath samples and a standard mixture of VOCs were run using capillary gas chromatography-mass spectrometry in the full scan mode.

The results showed no interference by Freons. The Freons were clearly separated from the VOCs of interest regardless of when the breath sample was collected. Appendix F shows the chromatograms.

2.9.3. Mouthpiece interference testing: All breath samplers had attached filtration mouthpieces commonly used for spirometry (Pulmoguard bacterial/viral filter, Queset Medical, Brockton, MA) to prevent microbiological contamination of the unit and re-entrainment by the subject. The microguards were tested by RTI and no evidence was found that the units led to absorption or interference with the target analytes.

2.9.4. Panel study run-in period: Recruited subjects performed daily tasks for 5-10 days before the start of air pollution monitoring on Nov. 4, 1999, except for one subject who did this for 3 days. This provided the opportunity for subjects to become familiar with the study procedures and for any problems in completing tasks to be resolved with field staff.

2.10. Data Management of Daily Asthma Diary

Microsoft Access data entry screens were programmed for the asthma diary for easier data entry by a coder. To prevent data entry errors, research assistants verified the keypunched data by re-reviewing records against original input. In addition to on-site validity checks during follow-up, data entered at the end of the panel was checked with SAS programs for missing data, outliers, and ambiguous, incomplete or invalid responses. For instance, a subject may record as-needed medication use but reports no symptoms. Descriptive analyses by individual subjects were used to identify potentially invalid diary data using various techniques to assess falsified paper diaries (discussed in Results section 4.2). Descriptive analyses for variables were used to determine the shape of the distribution, central tendency, temporal and spatial trends, exposure correlations, and intra- and inter-individual variability.

All raw data were archived under unique file names along with software programs and methods used to create and analyze new datasets. All program files were archived, linked to the data dictionary, and had key programming objectives embedded as program notes.

2.11. Exposure Assessment Methods

2.11.1. Overview

The objective of the exposure assessment component of the present study was to quantify breath VOCs in asthmatic children and to explore the relationships between breath, personal, indoor, and outdoor exposures, and personal activities. It provided a relevant point of reference to the companion panel study examining VOC exposures and acute asthma in children.

To collect breath samples in the field, the sample collection device should have four characteristics: ease of collection, portability, collects predominately alveolar air, allows for rapid collection (1-2 minutes). In the early 1990s, the team at the Research Triangle Institute developed such a device (Raymer et al., 1990), which had not previously been used in an epidemiologic study.

2.11.2. Exposure Assessment Study Design

Details of the overall study design and subject population are given in the Methods Sections 2.1 to 2.3. Here we only describe the exposure-related part. Twenty-seven subjects with a history of asthma were recruited by RLANRC to allow 10% of loss to follow-up. The final cohort consisted of 24 subjects, who were followed from October 25, 1999, to January 24, 2000. We instructed subjects to give breath VOC samples on the days when they had an asthma exacerbation (event samples) and at times free of symptoms (baseline samples). Daily activity diaries were also collected. Among these 24 subjects, a subset of 4 were selected to participate in an exposure assessment with daily personal exposure and indoor sample collection using VOC passive badges. Details of the sample collection results are shown in Table 2.1.

Table 2.1. Data collection results for exposure assessment

	Breath samples collected at onset of asthma exacerbations	Baseline breath samples collected on symptom-free days	Daily activity recorded using a diary	Passive badges for daily personal exposure	Passive badges for daily indoor exposure	Outdoor stationary monitoring
24 subjects	total=68 samples	total=78 samples	Min: 29 days Max: 74 days Total: 1355 person-days			3 months
Subset of 4 subjects	included in above rows	included in above rows	included in above rows	each collect 34 days total=136 badges	each collect 34 days total=136 badges	3 months

2.11.3. Time-Activity Diary (TAD)

Subjects recorded activities in diary cards separate from the Daily Asthma Diary. Activities were given by place, time of day and level of physical activity (Appendix G). Subjects were given a TAD designed as a booklet to be carried throughout the day in a pocket or small purse and filled out throughout the day. The cards were put in plastic diary pockets with punched holes to make the recording easier. Subjects were instructed to record spatial location, time indoors and outdoors, time in study area or outside area (referenced to a map given to them at baseline), the level of physical activity, and time in a motor vehicle and other locations relevant to VOC exposures (garage/gas stations, near smoker, laundromat, swimming pool, painting, hair salon, detergent use). The monitoring duration began when subjects awakened and continued until evening. The time resolution of the diary is 30 minutes.

At the in-home training session (discussed above) research assistants assessed the subjects' usual types of physical activities and related it to what should be entered in the TAD. Subjects were asked about the kind of major physical activities they do that are ≥ 1 hour, and how to interpret the level of physical exertion. For instance, playing baseball for 1 hour should yield no more than 30 minutes of moderate activity depending on the game and position.

2.11.4. Sample Collection

Samples were collected by the RLANRC team. RTI provided the sampling devices. Samples were collected and shipped to RTI via FedEx. Chain-of-custody sheets recording field information were shipped together with the samples. Upon receiving the samples, the mass spectrometry lab checked the labeling, seals, and the chain-of-custody sheet before analyzing the samples.

2.11.4.1 Sampling method

1. Breath Samples

- *Breath sampler:* The breath samplers were manufactured by RTI. Details were provided in a previously published paper (Raymer et al., 1990). Briefly, the participant inhales clean air through a one-way valve and exhales through a second one-way valve into a long Teflon tube, which is connected to an evacuated stainless steel SUMMA canister. Clean air for inhalation is provided via filtration of ambient air through carbon respirator cartridges. The device is designed in such a way that the air from the end of the expiration is drawn into the canister, which ensures that alveolar air is sampled. Except for the stainless-steel breath collection canister, all parts of the device are made from Teflon to minimize interference.

- *Sample collection:* Subjects were asked to collect breath samples at the onset of asthma exacerbations (event) and at times free of symptoms (baseline). The baseline attribute was instructed to subjects to mean no asthma symptoms that day or the previous two days. The 3-day time interval is based upon the resident times of the target compounds, which can extend to 3 days in the so-called 4th phase of VOC retention in adipose tissue (Wallace et al., 1990). The epidemiologic analysis section discusses our ability to obtain the samples in this manner. For each sample collection, two minutes sampling time was required to ensure a sufficient volume of breath air for quantification. When collecting the canisters, the field team would check the valve before removing the canister from the breath unit. If it was not tightened, the canister would be invalidated.

2. Indoor and Personal Samples

A 3M 3530 organic vapor passive badge with back-up section was used to collect personal and indoor samples from the subset of 4 subjects. The personal samplers were put on the collar of subjects to be close the breathing zone, and the indoor samplers were placed in the subjects' bedroom.

3. Outdoor Stationary Central Site Measurements

Two SCAQMD operated monitoring sites, Heliotrope and Nimitz, provided outdoor stationary monitoring results for VOCs. Methods are detailed in SCAQMD (2000). For VOCs, air samples were collected in canisters using the XonTech 910A and analyzed using GC/MS, EPA TO14 methodology.

The following data were collected for use in the epidemiologic study only. For the measurement of carbonyls, air samples were collected using the XonTech 920 carbonyl channel with a potassium iodide coated ozone denuder and a Waters silica gel cartridge impregnated with dinitrophenyl hydrazine and analyzed using EPA Method TO-11 (Winberry et al., 1988). Gravimetric PM_{10} was measured with quartz filters in SSI hi-volume samplers with a size selective inlet. Elemental and organic carbon (EC-OC)

analysis utilized the same quartz filters. EC-OC filter samples were analyzed by Desert Research Institute's Thermal/Optical analyzer. Continuous PM_{10} concentrations were measured with a tapered-element oscillating microbalance (TEOM). The TEOM is an inertial instrument that measures particle mass in real time on an exchangeable filter cartridge by monitoring frequency changes of a tapered element (Patashnick & Rupprecht, 1991). The PM_{10} data was used as 1-hr averaged data. The TEOM sampler inlet was operated at 16.7 L/min and the inlet air stream was heated to a constant 50 °C to keep water in the vapor phase. Criteria pollutant gases were monitored continuously using UV photometry for O_3, gas phase chemiluminescence for NO_2, ultraviolet fluorescence for SO_2 and non-dispersive infrared spectrophotometry for CO.

The Heliotrope station in Maywood provided outdoor measurements from Nov 4 to Dec. 20, 1999, whereas Nimitz provided outdoor measurements from Nov. 19, 1999 to Jan. 23, 2000. However, because the temperature provided by Heliotrope from Nov. 09 to Dec. 09, 1999 did not appear to be correct (around 0° F), we did not use the temperature measurements from Heliotrope during this period. On days when there were two valid measurements from the two stations, we pooled the measurements from the two stations. Otherwise, measurements from one of the stations were regarded as the outdoor measurements for all the subjects.

2.11.4.2. Sampling device and preparation of QA/QC samples

Before shipping the sampling devices to the field, RTI cleaned and examined the devices. In addition, we also prepared QA/QC samples. The following summarizes the work.

Items	Details
Breath sample collection devices	• 27 breath sample collection units manufactured and cleaned • 80 canisters purchased and cleaned. The flow rate for all the canisters was calibrated. The flow rate of about 5% of the randomly selected canisters was examined after calibration.
Indoor and personal badges	• 500 3M badges were purchased. Color coding system was developed to enable a badge to sample 24-hour integrated exposures (48 hours normally required) • Quality control samples -- 5% of the samples were spiked with known amount of target analytes for analytical quality control
Diary pockets and cards	• 27 diary pockets were made to protect the diary cards yet be convenient enough to record activities every 30 minutes • Diary cards with icons were developed and made to facilitate diary recording
Questionnaire	Baseline exposure questionnaire was developed

2.11.5. Sample Analysis

Canisters were analyzed using a 16-position canister autosampler (Entech Instruments, Inc., Model 7016A), which was connected to GC/MS (Hewlett Packard Model 5972). Badge samples were extracted with acetone/carbon disulfide and analyzed by GC/MS (Hewlett Packard Model 5988A). Details of the sample analysis are provided in the standard operating procedure in Appendix H.

2.11.6. Quality Assurance

2.11.6.1. Sample Collection

One of the most important aspects to ensure a high-quality sample collection is the preparation of the sampling device. The breath-sampling device manufactured in RTI was cleaned, checked with seals before shipping to the field team in RLANRC. Canisters were cleaned before each shipment. Backgrounds of each batch were checked to ensure the canisters were thoroughly cleaned. The flow rate of the orifice of each canister was also checked and recorded.

Each canister was tracked in the field and during analysis using a unique ID. In this study, RTI provided a total of 78 canisters. Each made 1, 2, or 3 trips to the field and back. None of the canisters malfunctioned.

2.11.6.2. Sample Analysis

1. Calibration

Prior to analysis of the samples, six calibration standards were used to construct a calibration curve for each target analyte, covering the expected target analyte concentration range of the samples. The lowest-concentration calibration standards were at or near the estimated method detection limit for each analyte. Response factors (RF) and percent differences for each analyte were calculated using the octanfluorotoluene as internal standard. If the relative standard deviation (RSD) calculated from the multipoint calibration solutions for any analytes exceed 25%, either additional aliquots of calibration solution were analyzed to obtain an acceptable RSD of RFs, or action was taken to improve GC/MS performance.

In addition to the initial calibration, calibration checks were performed at the beginning of each 8-hour work shift and after analyzing the last sample in a batch and at the end of each analysis run. The RF for each analyte would be considered acceptable if RFs were within ± 25% for all primary targets and no more than 2 secondary targets were out-of-control. If the criteria were not met, the samples were reanalyzed. All suspect data (the analytes that did not meet the calibration check) were identified in laboratory records and the data report.

2. Data Management

To limit entry errors, an information shell containing the frame of the information was first constructed to ensure the linkage of the datasets. Data entry screens with error protection features were also programmed for data entry. Professional data entry personnel keyed in diary data and baseline questionnaire data, whereas canister and badge measurement data were reduced from mass spectrometry outputs directly.

During the data entry, about 10% of the diaries were double entered for quality checks. Principal investigators checked analytical data. The quality assurance officers in the Analytical and Chemical Science unit also audited breath and badge measurement data. Records and laboratory notebooks were carefully reviewed. Algorithms used for data reduction were checked by back calculating some randomly selected concentrations using the areas of primary ion and information from the calibration curve. Calibrations, response factors, performance evaluation, and method detection limit were examined. The QA check also extended to the matching of the electronic file and the raw data, the instrument logbook, etc.

Statistical analysis and modeling were performed by Dr. Hu with input on modeling approaches from RTI statisticians. SAS codes were double-checked before applying them to data analysis.

2.12. Statistical Analysis of Exposure Assessment Data

2.12.1. Descriptive Statistics

We began with a statistical analysis by generating descriptive statistics for all the exposure variables, including VOC measurements in breath canisters, badges, and variables in diaries. SAS STAT (SAS 8.2, Cary, NC) was used for descriptive statistical analysis, and S-Plus (Insightful, Seattle, WA) was used to generate the plots.

2.12.2. Relationships between personal VOC exposures, indoor exposures, outdoor exposures, and other exposure sources (Specific Aim 2)

Analysis of the relationships between personal VOC exposures, indoor exposures, outdoor exposures, and other exposure sources were based upon data collected from the subset of 4 subjects. Each person's exposure was modeled separately to examine the differences among the individuals. Then we pooled the measurements from the 4 subjects to find more generalizable models.

A key assumption for ordinary least squares (OLS) regression analysis is that the errors are independently and identically distributed. The data sets collected from the 4 subjects, however, are longitudinal and autocorrelated, therefore, OLS regression analysis cannot be used. Instead, we conducted time-series analysis. We first analyzed the autocorrelation of the series. Then we used the autoregressive integrated moving average (ARIMA) method developed by Box and Jenkins (Box and Jenkins, 1976) to fit the time-series model. Other environmental scientists have used this method to investigate air pollution and mortality because of its flexibility in cooperating stochastic independent variables (Shumway and Stoffer, 2000).

The basic model format used to model the relationship is described as follows:

$$Y_t = a + \sum_{J=0}^{l} b_j Y_{t-j} + \sum_{J=0}^{m} c_j IE_{t-j} + \sum_{J=0}^{n} d_j OE_{t-j} + \sum_{J=0}^{p} \beta_j X_{t-j} + E_t$$

Where

Y_t = personal exposure (or breath VOCs) for day t

IE_{t-j} = indoor exposure for (t-j) th day, where t-j is the lag from day t

OE_{t-j} = outdoor exposure for (t-j) th day, where t-j is the lag from day t

X_{t-j} = vector of covariates from personal activity diary, including eight activities that potentially result in high VOC exposures, including doing laundry, being at a gas station, near smokers, swimming, in hair/beauty salon, in a motor vehicle, using house-cleaning products, and painting.

E_t=autocorrelated noise term

This time series regression model allows the target series, personal exposure Y_t, to depend on its own past values, current and past values of explanatory variables for indoor exposure (IE) and outdoor exposure (OE). It also allows for the inclusion of other personal activities X as explanatory variables.

We used procedures described by Brocklebank and Dickey (1986). Briefly, we first checked the autocorrelation of the independent variables. Then we identified univariate models for each autocorrelated independent variable to obtain the goodness of fit required to yield white-noise residuals. Models constructed for each independent variable were then applied to the outcome variable, personal exposure (PE) to obtain the residuals. The cross-correlation functions (CCF) between the residuals were then calculated. Next, a transfer function model was fit with no structure on the noise term. The residuals from this model were examined. Finally, the full model, with transfer function and noise term, was fit to the data (SAS 1999; Brocklebank and Dickey, 1986). Forward procedure was used throughout the analysis in incorporate other predictor variables such as being at a gas station, painting, etc. All variables that were not significant ($p > 0.05$) were excluded. The residuals of the final model were checked to ensure no further fitting was needed.

2.12.3. Breath VOC

Analysis of breath VOC measurements focused on two areas: (1) the within- and between-individual variances, and (2) the correlation between breath VOC and outdoor concentrations.

2.12.3.1. Within- and between-individual variances

We used the following random-effect ANOVA model to analyze within- and between-individual variances. This method has been used by many researchers to assess occupational exposures (Kromhout & Heederik, 1995). Because the distributions of the concentrations were highly skewed, we first log-transformed the exposures.

$$Y_{ij} = Ln(X_{ij}) = u + \beta_i + \varepsilon_{ij} \quad \text{for } (i = 1,2,....k) \text{ and } (j = 1,2,....n_j)$$

Where

X_{ij}=breath VOC concentrations of ith subject on jth day

u=mean of Y_{ij}

β_i=random deviation of the ith subject's true breath VOC from u

ε_{ij}=random deviation of the ith subject's breath VOC on ith day from his true measurement

In this model, β_i and ε_{ij} are assumed to be independent of each other and normally distributed: i.e., $\beta_i \sim N(0, \sigma_B^2)$ and $\varepsilon_{ij} \sim N(0, \sigma_w^2)$.

Because of the unbalanced data, PROC GLM (SAS 8.2, Cary, NC) was used to calculate the within- and between-individual variances. Table 2.2 delineates how the within- and between- individual variances were calculated and compared.

Table 2.2. Within- and between- individual variances

Factor	Sum of Squares	DF	Mean Squares	Expected Values
Individual	$SS_{between}$	**k-1**	$MSE_{between}=SS_{between}/k-1$	$\sigma_w^2+n_0\sigma_B^2$
Error	SS_{error}	**N-1**	$MSE_{within}= SS_{error}/N-k$	σ_w^2

k-number of individuals
N-total number of observations

Because SAS produced σ_w^2 in its output, i.e., $\sigma_w^2 = MSE_{within}$, σ_w^2 can be obtained easily. However, σ_B^2 has to be calculated from the output using equation $MSE_{between}=\sigma_w^2+n_0\sigma_B^2$. For unbalanced data as in this study, n_0 was calculated using the following formula (Kleinbaum et al., 1988):

$$n_0 = \frac{\sum_{i=1}^{k} n_i - (\sum_{i=1}^{k} n_i^2 / \sum_{i=1}^{k} n_i)}{k-1}$$

Where n_i is the number of measurements for each subject.
Corresponding geometric standard deviations were calculated using $S_w=\exp(\sigma_w)$ and $S_B=\exp(\sigma_B)$.

2.12.3.2. Relationship between breath VOCs and outdoor concentrations

Data collected from the 24 subjects were used to analyze the relationship between breath VOCs and outdoor concentrations. The measurements of the 24 subjects were pooled together and averaged by date. This yielded a fairly complete time-series with a few missing points, which were filled using linear extrapolation. The same time-series analysis strategy described earlier was used to analyze the relationships. Indoor and personal exposures were not included in the model because the data were collected from only 4 subjects.

2.12.4. Correlations between the VOCs

Because the distributions were not normal, Spearman's correlation between the VOCs in outdoor air and breath samples were analyzed and calculated.

2.12.5. Missing Data

Because missing data result in unreliable results, substantial effort was made to impute the missing data, using two methods: (1) logical imputation using common knowledge and (2) interpolation. In situations when these two were impossible, we left the data missing and did not include them in analyses. In the activity diaries, the most common missing data were the subjects' location between late evening and early morning when the children were asleep. In these cases, we examined the locations of the last entry in the evening and the first entry in the next morning and filled the gap. For other time intervals, which we could not decide upon, an "unknown" category was created for the missing data. The data collected for the group of 4 subjects were nearly complete for personal and indoor measurements for the 34 days of study period. Only 2 missing days were found in one of the 4 subjects. In this case, we used the measurements of the adjacent days to interpolate the measurements of the missing days. Another interpolation was done for the pooled breath measurements. To explore the relationship between breath

VOCs and outdoor measurements, the breath VOCs of all the subjects in the 24-subject group were pooled together to form an 81-day time series. Among the 81 days, 19 (23%) days had no canister collection and these days were scattered among the 81 days with the largest gap of 2 days. To interpolate the missing data in the time-series, we used PROC EXPAND in SAS before analysis. Note that for epidemiologic analysis, only non-missing exposure data were used, i.e., no data were interpolated.

2.13. Statistical Analysis of Relationships Between Exposures and Health Responses

2.13.1. Longitudinal Regression Analyses of Symptom Data:

The regression analysis of pollutant effects on asthma symptoms reported in the diary was initially based on three dichotomous outcome variables with various cutoff points across the asthma symptom score. The first is for the reported presence versus absence of <u>any asthma symptoms</u> (score = 0 versus score > 0). It is important to note that for this variable, symptoms not considered by the subject to be bothersome (score=1) are not likely to be clinically relevant.

The second was a dichotomous asthma symptom variable with a cutoff point between a score of 1 and 2. This variable represented the risk of asthma symptoms that were <u>bothersome or more severe</u> as compared with no symptoms or symptoms not bothersome.

The third was a dichotomous response variable representing the occurrence of an asthma episode with a clinical impact on the subject's daily life in that it <u>interfered with daily activities</u>:

<u>no episode:</u> no asthma symptoms, symptoms not bothersome or not interfering with daily activities (score < 3), versus

<u>episode:</u> symptoms that interfered somewhat with daily activities or were more severe (score ≥ 3).

This was not necessarily the same as a so-called "asthma event," defined for the purposes of collecting VOC breath canisters. Recall that an asthma event was defined for subjects as asthma symptoms that required the use of as-needed rescue medications, generally metered dose ß-agonist inhalers, as opposed to no symptoms at all, in which case the breath sample was referred to as a "baseline" sample. We expected subjects would give exhaled breath samples for asthma events during reports of either bothersome symptoms or asthma episodes that interfered at least somewhat with daily activities.

This approach of using a clinically relevant symptom outcome has been successful in detecting large and robust pollutant associations in sensitive subpopulations of asthmatics studied in previous asthma panels (Delfino et al., 1996; 1997; 1998; 2001a; 2001b).

Effect estimates for asthma symptoms will be expressed as odds ratios with 95% confidence intervals. We utilized the generalized estimating equation (GEE) for regression analyses of the symptom variables. The GEE was developed by Liang and Zeger (1986) for non-normal response data (e.g., binary) that are discrete and correlated (within-individual clusters). Repeated daily measurements over time in individuals constitute a cluster of observations. GEE models the covariance structure of the correlated (not independent) measurements in estimating the p ×1 vector of regression parameters β, given by:

$$S(\beta) = \sum_{i=1}^{K} \frac{\partial \mu'_i}{\partial \beta} V_i^{-1} (Y_i - \mu_i(\beta)) = 0$$

Where

$\frac{\partial \mu'_i}{\partial \beta}$ is the $p \times n_i$ matrix of partial derivatives of the mean with respect to the regression parameters for the ith subject (i = 1, ... , K).

$\boldsymbol{V}$ is the covariance matrix of $\boldsymbol{Y}$, and

$\boldsymbol{Y} = [Y_{i1}, \ldots, Y_{ini}]'$ is the vector of outcome measurements on the ith subject for n_i measurements (j = 1, ... , n_i) with a corresponding vector of means $\boldsymbol{\mu}_i = [\boldsymbol{\mu}_{i1}, \ldots, \boldsymbol{\mu}_{ini}]'$,

The GEE model is conceptually a set of separate regression equations on repeated measurements in each individual. Therefore, every subject can act as his or her own control. This statistical model fits the design of the study, which is based on daily repeated measurements of acute asthma status, which can vary markedly from day to day. The GEE models were tested using the logit link in the SAS generalized linear model procedure Genmod, version 8 (SAS, 1999). The Genmod procedure uses a ridge-stabilized Newton-Raphson algorithm to maximize the log likelihood function for the regression parameters. This GEE approach to linear regression modeling is well-suited to panel data because: 1) it can be applied to repeated measures that are unbalanced, have unequal numbers of observations in different individuals, or have missing observations; and 2) it accounts for temporally correlated responses and the dependence of repeated observations in single individuals. For analyses of breath samples, there was no significant serial correlation because breath samples were collected many days apart. For analyses of daily ambient data, serial correlation was found and accounted for to prevent bias in the estimation of statistical significance. The working correlation was modeled as autoregressive lag 1 (AR1)

Regression models for VOCs and for the other pollutants were tested for confounding by day-of-week time trends, weather, and respiratory infections. Generally, confounding was considered to be a 15% change in the regression parameter estimate for the exposure of interest. The fit of the models were tested with deviance statistics.

The effects of air pollutant concentrations on the same day (exposure lag 0) and on days prior to the day of the diary symptom report were examined. This was accomplished by regressing symptoms on pollution levels measured on up to 4 days prior to the day of symptom reporting (exposure lag 1 to lag 4).

Independent effects were examined for individual VOCs and for criteria air pollutant gases (O_3, NO_2, CO and SO_2). Confounding and interaction between the various air pollutants were tested. Two-pollutant regression models were tested by including an individual VOC with a criteria air pollutant gas. Only 12-17 out of 24 days overlapped for both gravimetric data and criteria gases. Because of this limitation in SCAQMD data, 2-pollutant models for PM only included the PM variables themselves, namely, PM_{10}, total organic carbon and total elemental carbon. This was to determine whether effects of EC or OC were confounded by PM_{10} and whether effects of PM_{10} were confounded by EC or OC.

2.13.2. Longitudinal Regression Analyses of PEF Data:

Lag pollutant models did not show any association between evening PEF deficits and lagged exposures or between morning PEF deficits and exposures 2 days in the past. Therefore, for simplicity, regression models will be presented separately for morning and evening PEF in relation to exposures on the same day for evening PEF and the previous day for morning PEF. For breath VOCs, evening PEF was regressed on VOC concentrations on the day subjects performed the breath-sampling maneuver (lag 0) and morning PEF from the following day was regressed on the same breath VOC concentrations, which are then referred to as exposure lag 1.

For multiple regression analyses of PEF we employed the general linear mixed model, which estimates both fixed and random effects (Littell, 1996) and is particularly suitable for correlated data in individuals (Jennrich, 1986). We used the SAS Mixed procedure, version 8 (SAS, 1999) that optimizes a restricted maximum likelihood function by using the Newton-Raphson algorithm (Littell, 1996**;** Lindstrom & Bates, 1988). The mixed model expands the standard linear regression model to a random effects model as follows**:**

$$\mathbf{Y_i} = \mathbf{X_i}\,\boldsymbol{\beta_i} + \mathbf{Z_i}\,\boldsymbol{\upsilon_i} + \boldsymbol{\varepsilon_i}$$

Where

Y is the vector of dependent observations,
X is the known matrix of values of independent variables,
β is the vector of regression parameters,
υ is an unknown vector of random effects with known model matrix Z,
$\boldsymbol{\varepsilon}$ is an unknown random error vector that is no longer required to be independent,
and the *i*'s denote that the observations and known matrixes are specific to each subject (Laird & Ware, '82).

Random intercepts were estimated for each individual to indirectly control for anthropomorphic differences that could lead to lung function differences. For analyses of breath samples, there was no significant serial correlation because breath samples were collected many days apart. For analyses of daily ambient data, serial correlation was found and accounted for with AR1 autoregressive parameters to prevent bias in the estimation of statistical significance.

Regression models for VOCs and for the other pollutants were tested for confounding by day-of-week time trends, weather, and respiratory infections. Generally, confounding was considered to be a 15% change in the regression parameter estimate for the exposure of interest. The fit of the models were tested with Akaike's information criterion (AIC). Two-pollutant models were also tested for PEF as described above for symptom models.

3. RESULTS OF THE EXPOSURE ASSESSMENT STUDY

3.1. Field Compliance

One of the purposes of this study was to investigate the potential utilities as well as problems of using canisters and other exposure sampling devices in a longitudinal study for children. Because the canisters have never been used in an epidemiological study, we made a substantial effort to check the field compliance. The compliance of diary recording was also examined.

3.1.1. Breath VOC (Specific Aims 2.a)

A total of 146 breath canisters were collected in this study. Seventy-one were collected in November 1999, 43 in December 1999, and 32 in January 2000. On most of the days, 0-3 canisters were collected from the panel, except on November 1 and 2, 1999, when 9 and 11 canisters, respectively, were collected. The 9 canisters collected on November 1, 1999 were all baseline canisters, while 6 of the 11 collected on November 2, 1999 were event canisters.

Three subjects submitted only 1 canister during the entire study period. Nine subjects submitted 8 or more. The canister collection by subject ID is summarized in Table 3.1.

An important requirement in the breath samples was that baseline samples be collected at least 3 days after the event or report of asthma symptoms and during these 3 days, there should not be any symptoms. We therefore checked the time between the event and baseline samples. A minimum of 3 days were found between all event and baseline samples except for 3 cases (ID 2471, 2485, and 2491) in which the baseline and event samples were 2 days apart. In the Epidemiologic Section, the UCI team reports that some of the subjects did not record their symptom diary as required and thus were excluded from analysis. However, because there was no evidence that they falsified the breath samples, we included all available breath data from the 24 subjects in the breath VOCs analysis. In cases where diary information was needed for modeling, however, these subjects were excluded from the analysis.

3.1.2. Time activity diaries (TAD)

Daily activity diaries were collected from 24 participants. By the 4th day (October 28, 1999) of the panel study, most subjects (> 20) had started their TAD. The majority of the participants (all but one subject) did not record their activity during the period of December 22-26, 1999. Ten subjects volunteered to continue to record data into TADS after Christmas.

The total number of TADs collected from each subject ranged from 29 to 77. For 10 subjects from whom the data collection extended beyond Christmas, an average of 66 TADs were collected. Table 3.2. summarizes the total and percent completion of the TADS for each subject. The percent completion for the 24 subjects was 75.

Table 3.1. Number of breath canisters collected by subjects

Subject ID	Total Number of Canisters	Number of Baseline Canisters	Number of Event Canisters
2468	9	5	4
2469	10	5	5
2470	4	3	1
2471	2	1	1
2472	10	5	5
2473	4	2	2
2474	9	4	5
2483	6	4	2
2484	3	2	1
2485	4	2	2
2486	1	0	1
2487	4	2	2
2488	8	5	3
2489	4	2	2
2490	9	4	5
2491	6	3	3
2492	3	2	1
2493	1	1	0
2494	6	3	3
2495	2	1	1
2496	14	7	7
2497	11	7	4
2498	1	1	0
2499	2	1	1
2500	3	1	2
2501	10	5	5

Table 3.2. Total and missing dates in TADs

Subject ID	Total Number of Days in Study	Number of Days with TADs	% Completion
2468	90	77	86
2469	71	55	77
2470	58	36	62
2472	88	74	84
2473	55	34	62
2474	88	57	65
2483	84	63	75
2484	48	34	71
2485	55	29	53
2486	55	46	84
2487	55	53	96
2488	91	70	77
2489	53	37	70
2490	77	70	91
2491	88	72	82
2492	55	49	89
2494	56	55	98
2495	54	52	96
2496	88	74	84
2497	87	58	67
2498	53	53	100
2499	52	46	88
2500	54	54	100
2501	80	74	93
Mean	62	51	75

3.2. QA/QC Results

3.2.1. Precision

Table 3.3 lists the precision calculated as relative standard deviation (% RSD), defined as standard deviation/mean. The results indicated a satisfactory %RSD for the primary ion used to quantify the target analytes.

Table 3.3. Precision

Analytes	% RSD
1-bromo-4-fluorobenzene 174	0
1-bromo-4-fluorobenzene 95	5
Methylene chloride 84	10
Methylene chloride 86	27
1,1-Dichloroethane 63	11
1,1-Dichloroethane 65	15
Chloroform 83	11
Chloroform 85	22
Carbon tetrachloroethylene 117	9
Carbon tetrachloroethylene 121	8
Benzene 78	10
Benzene 77	23
Toluene 91	7
Toluene 92	7
Tetrachloroethylene 166	6
Tetrachloroethylene 129	9
m,p-Xylene 91	4
m,p-Xylene 106	5
o-Xylene 91	5
o-Xylene 106	2
Styrene 104	4
Styrene 78	14
p-Dichlorobenzene 146	6
p-Dichlorobenzene 148	6
o-Dichlorobenzene 146	5
o-Dichlorobenzene 148	6

3.2.2. Limit of detection (LOD)

The limit of detection in this study was defined as the minimum concentration of an analyte that can be measured and reported with 99 % confidence that the concentration is greater than zero. The LOD was determined by multiplying the one-sided 99% student's t-statistic ($t_{0.99}$) of n-1 degrees of freedom by the standard deviation (SD) of blanks.

$$LOD = t_{0.99} \times SD_{blank}$$

The LODs for canisters and badges are shown in Tables 3.4 and 3.5.

Table 3.4. Limit of detection (LOD) for canisters

Chemicals	LOD (ng/L)
1,1-Dichloroethane	0.27
Benzene	0.39
Carbon tetrachloride	0.32
Chloroform	0.45
Methylene Chloride	0.98
Styrene	0.36
Tetrachloroethylene	0.48
Toluene	3.99
M, p-Xylene	0.17
o-Dichlorobenzene	0.44
o-Xylene	0.22
p-Dichlorobenzene	0.31

Table 3.5. Limit of detection for badges

Chemicals	LOD (ng/L)
1,1-Dichloroethane	1.67
Benzene	1.23
Chloroform	0.83
Styrene	7.31
Tetrachloroethylene	1.72
Toluene	6.94
M, p-Xylene	2.04
o-Dichlorobenzene	1.57
o-Xylene	6.81
p-Dichlorobenzene	0.41

3.2.3. Field blanks

Field blanks are unexposed charcoal badges or canisters that were shipped from RTI to the field and shipped back with the rest of the samples. The results of these analyses help define contamination resulting from field sampling and transportation and lot-to-lot variations. There were 15 field badge blanks and 8 field canister blanks. The analytical results of the field blanks are shown in Tables 3.6 and 3.7.

Table 3.6. Blank canister measurement results

Chemicals	N[b]	Concentrations (ug/L)
1,1-Dichloroethane	13	ND[a]
Benzene	9	ND
Carbon tetrachloride	8	ND
Chloroform	13	ND
Methylene Chloride	5	ND
Styrene	13	ND
Tetrachloroethylene	13	ND
Toluene	13	ND
M, p-Xylene	13	ND
o-Dichlorobenzene	13	ND
o-Xylene	13	ND
p-Dichlorobenzene	13	ND

[a] ND – below limit of detection
[b] N – number of observations. N is greater than 8 because some duplicate samples were analyzed.

Table 3.7. Blank badge measurement results

Chemicals	N[b]	Concentrations (ug/L)
1,1-Dichloroethane	20	ND[a]
Benzene	20	ND
Chloroform	20	ND
Styrene	20	ND
Tetrachloroethylene	20	ND
Toluene	13	ND
M, p-Xylene	20	ND
o-Dichlorobenzene	20	ND
o-Xylene	20	ND
p-Dichlorobenzene	20	ND

[a] ND – below limit of detection
[b] N – number of observations. N is greater than 15 because some duplicate samples were analyzed.

3.2.4. Field controls

Field controls are samples spiked with known quantities of target analytes. They were shipped from RTI to the field and back with the rest of the samples. The results of these analyses were used to assess the overall recovery of the target analytes. There were 29 field badge controls and 6 field canister controls. The results of the field controls are shown in Tables 3.8 and 3.9. The recoveries for the canister controls

were good (between 87% to 127%) except for methylene chloride, which had a recovery of 139%. The reasons for this are not clear since none of the field blanks were found to contain this compound and canisters tested after cleaning and before shipment to the field where clean. This compound was sometimes found to be out of control (high) during routine analysis of calibration check standard (in these cases, the data were flagged and not included in data analysis). Thus, data for this compound need to be interpreted cautiously. The recoveries for the badges were low for benzene, chloroform, toluene, and o-xylene (Table 3.9) yet with very good consistency (RSD<12%). Given acceptable recoveries of the standard reference materials (Table 3.10), we think the low recoveries in badges were most likely caused by the loading problems that occurred while preparing the field controls. Therefore, the analysis of the field samples should be reliable.

Table 3.8. Recoveries of the field canister controls.

Chemicals	Spike Level (ng)	Mean Measurement (ng)	Recoveries (%)	RSD[a]
1,1-Dichloroethane	1.60	1.81	113	27
Benzene	1.29	1.54	119	43
Carbon tetrachloride	2.49	2.52	101	6
Chloroform	1.95	2.47	127	28
Methylene Chloride	1.36	1.89	139	37
Styrene	1.74	1.77	102	21
Tetrachloroethylene	2.68	2.32	87	21
M, p-Xylene	3.42	3.43	100	18
o-Dichlorobenzene	2.38	2.07	87	21
o-Xylene	1.72	1.58	92	21
p-Dichlorobenzene	2.38	2.13	89	17

[a]Relative standard deviation of recoveries

Table 3.9. Recoveries of the field badge controls.

Chemicals	Spike Level (ng)	Mean Measurement (ng)	Recoveries	RSD[a]
Benzene	16714.16	9069.42	54	7
Chloroform	11382.94	7439.86	65	8
Tetrachloroethylene	10223.16	8954.48	88	11
Toluene	15399.68	9169.13	60	8
m, p-Xylene	15808.76	13769.76	87	12
o-Xylene	7235.32	3286.99	45	6

[a]Relative standard deviation of recoveries

Table 3.10. Percent recoveries of SRM

Analytes	N	Mean	SD	Min.	10th percentile	25th percentile	Median	75th Percentile	90th percentile	Max.
Benzene	13	75	6	64	69	72	75	78	81	86
Toluene	13	71	6	61	63	67	72	74	78	80
p-Dichlorobenzene	13	72	9	50	66	70	73	74	82	86

3.2.5. Standard reference materials

We also used standard reference material (SRM) from NIST to evaluate the performance. Thirteen replicates were run, which provided information on method accuracy (% recovery) and precision. The recovery distribution is shown in Table 3.10.

3.2.6. Duplicate analysis

For both canisters and badges, duplicates were analyzed to check the precision of the analytical procedures. Twenty-three duplicate samples were run in canister analysis, and 20 duplicate injections were run in the badge analysis. The coefficients of variation (CV) are given in tables 3.11 and 3.12. The results indicate excellent precision for both breath canister analysis and badge analysis.

Table 3.11. Coefficients of variation (CV) of duplicate samples of breath canisters

Chemicals	Mean CV
Benzene	11.4
Carbon tetrachloride	3.7
Chloroform	11.4
Methylene Chloride	19.9
Styrene	11.13
Tetrachloroethylene	13.2
Toluene	11.1
m, p-Xylene	8.08
o-Xylene	10.4
p-Dichlorobenzene	13.4

Table 3.12. CV of duplicate injection of badge samples

Chemicals	Mean CV
Benzene	1.9
Chloroform	3.4
Styrene	1.6
Tetrachloroethylene	2.7
Toluene	2.7
m, p-Xylene	1.5
o-Xylene	1.3
p-Dichlorobenzene	1.4

3.3. Descriptive Analysis

3.3.1. Indoor/outdoor hours

One piece of important information recorded in the diary is the location of the subjects. Five categories of activities were identified: (1) indoors in the Huntington Park (HP) area, (2) outdoors in the HP area, (3) indoors not in the HP area, (4) outdoors not in the HP area, and (5) in cars. Subjects who reported little time indoors in the HP area (2483, 2491, 2495, 2501) lived in the study region, but not in the city of HP

(2 in Maywood and 2 in Florence). The results are summarized in Table 3.13. In general, this cohort spent an average of 19.2 hours indoors, 2.8 hours outdoors, and 5 minutes in cars each day. About 1.85 hours are unknown (missing data). This result agrees with findings in a previous study in children in California (Liu et al., 1997). Although there appeared to be some difference between weekdays and weekends for some participants, the paired t-test indicated that the difference between weekdays and weekends was not statistically significant.

Table 3.13. Average indoor, outdoor, and in-car hours reported in the diary

	Weekdays						Weekends					
ID	Indoors in HP	Indoors not in HP	In Car	Outdoors in HP	Outdoors not in HP	Unknown	Indoors in HP	Indoors not in HP	In Car	Outdoors in HP	Outdoors not in HP	Unknown
2468	21.01	0.00	0.02	2.05	0.01	0.91	21.62	0.00	0.00	0.78	0.71	0.89
2469	20.17	0.00	0.01	2.49	0.00	1.33	20.78	0.00	0.00	1.73	0.06	1.43
2470	17.94	0.00	0.00	5.30	0.21	0.55	14.16	0.00	0.00	4.81	1.91	3.13
2472	18.97	0.00	0.01	4.19	0.17	0.67	17.98	0.68	0.00	3.52	0.35	1.47
2473	19.07	0.00	0.02	1.62	0.53	2.76	18.10	0.00	0.06	1.16	0.81	3.87
2474	19.73	0.00	0.06	2.19	0.24	1.78	21.37	0.00	0.06	1.50	0.38	0.69
2483	2.00	16.46	0.00	0.09	4.44	1.01	1.76	15.74	0.08	0.00	4.07	2.36
2484	19.19	0.00	0.00	4.05	0.00	0.75	19.50	0.00	0.00	4.43	0.00	0.08
2485	15.23	0.00	0.20	1.26	1.56	5.75	14.86	0.00	0.00	0.43	1.46	7.25
2486	17.78	0.00	1.07	3.96	0.18	1.00	16.15	0.96	1.21	3.21	1.25	1.23
2487	16.12	0.00	0.19	0.78	1.69	5.22	19.80	0.00	0.25	0.86	0.46	2.62
2488	21.24	0.00	0.07	2.17	0.18	0.35	15.30	0.00	0.75	2.83	4.95	0.18
2489	20.03	0.00	0.03	0.65	0.05	3.23	21.01	0.00	0.00	1.41	0.00	1.58
2490	17.35	0.00	0.04	1.96	0.92	3.72	18.94	0.00	0.02	3.18	0.52	1.33
2491	0.70	20.80	0.00	0.93	0.45	1.13	0.70	19.92	0.00	0.98	0.24	2.17
2492	18.44	0.34	0.01	4.01	0.00	1.19	19.76	0.00	0.18	3.80	0.00	0.26
2494	19.36	0.00	0.02	3.93	0.04	0.64	18.95	0.00	0.00	2.86	0.13	2.07
2495	0.00	19.59	0.01	1.80	0.80	1.80	0.00	19.92	0.00	3.13	0.04	0.92
2496	18.28	0.00	0.03	1.36	0.86	3.47	16.44	0.77	0.02	0.89	1.20	4.68
2497	21.02	0.00	0.01	1.26	0.10	1.61	21.12	0.00	0.00	0.94	0.08	1.86
2498	21.07	0.00	0.04	0.24	1.40	1.25	20.96	0.00	0.00	0.32	1.18	1.54
2499	20.16	0.00	0.00	1.28	0.49	2.06	19.48	0.00	0.00	0.75	1.42	2.35
2500	18.51	0.88	0.00	3.01	0.11	1.49	14.82	4.14	0.00	1.63	0.68	2.73
2501	0.00	18.76	0.01	1.08	0.72	3.43	0.00	21.88	0.00	0.06	1.54	0.52

3.3.2. Other exposure sources

Subjects were asked to record 7 sources of VOC exposures, including being in a laundromat, a gas station/garage, near a smoker, in a hair salon, swimming, and painting. Table 3.14 summarizes the total hours of these exposures.

Table 3.14. Hours spent in a laundromat, at a gas station, in a hair salon, near a smoker, swimming, and painting during the study period.

ID	Number of days with diary entry	Detergent Use	Gas Station	Laundro mat	Near Smoker	Staying in Hair Salon	Painting	Swimming
2468	67	0	0	42.5	8	0	0.5	0
2469	55	2.5	6.5	12.5	5	1	0	1
2470	36	2.5	1	0	0	0	1.5	0
2471	42	0	2.5	0	1.5	0	0	0.5
2472	74	0	0	7	8.5	3.5	0	0
2473	34	1	0	0	2.5	0.5	0	0
2474	57	8	2	1	0	0	0	0
2483	63	0	1	0	1	0	0.5	0
2484	34	0	1.5	10	1	0	0	0
2485	29	15.5	4.5	9.5	0.5	1.5	0	1
2486	46	5.5	3.5	7.5	3.5	12	1	3
2487	53	0	3	0	3.5	0	0	0
2488	70	0	1	0	0	0	0	7.5
2489	37	8	0.5	21.5	0	0	1.5	1
2490	70	0	2	5	3.5	0.5	0	0
2491	72	0	1.5	1.5	0	0	0	4.5
2492	49	0	2	7.5	1.5	0	0	0
2494	55	0	13	1.5	9	0.5	0	1.5
2495	52	25.5	3.5	0.5	12.5	1	0	0
2496	74	21.5	4	0.5	0	0.5	0	0
2497	58	2.5	1	0	7	0	1.5	0
2498	53	4.5	0	0	0	1.5	0	0
2499	46	0	1	4	1.5	1	0.5	0
2500	54	0	0	0	0	0.5	0	0
2501	74	0	1	1	0.5	0	0	0

3.4. Relationships between personal VOC exposures, indoor exposures, outdoor exposures, and other exposure sources (Specific Aims 2.b & 2.c)

3.4.1. Personal and indoor VOCs

Personal and indoor exposures were estimated from passive VOC badges collected from 4 selected subjects. The subjects started the badge sampling on November 16, 1999, and ended on December 19, 1999. Thirty-three badges were collected from subject 2496 and 2497. Thirty-one were 32 were collected from 2373 (one missing day) and 31 were collected from 2474(two missing days). In all, 129 personal passive badges and 129 indoor badges were collected from the subjects. No badges were collected on November 17, 1999 for all the subjects because of subjects' confusion of the two-badge

collection scheme (the subjects were asked to wear two badges on the collar). In addition to November 17, subject 2474 did not comply the sampling schedule on Dec. 14 and 15 therefore badges from these two days were excluded for analysis.

The descriptive statistics for the badges are shown in Table 3.15. Except for two chemicals (1,1-dichloroethane and o-dichlorobenzene), the percent measurable for the rest of the target compounds was above 60%. The results in Table 3.15 indicate that for these four subjects, the average personal exposure and indoor exposure were very close during the study period.

Table 3.15. Descriptive statistics for badge data

	Personal Exposure			Indoor Exposure		
	Percent Measurable	Mean(ng/L)	Std Dev.	Percent Measurable	Mean(ng/L)	Std Dev.
1,1-Dichloroethane	1.5	1.67	0.52	0.7	1.67	0.52
Benzene	99.3	12.93	9.21	98.5	12.60	9.04
Chloroform	72.6	3.17	2.88	72.6	3.11	2.42
Styrene	63.7	7.26	2.68	65.9	7.13	2.21
Tetrachloroethylene	74.1	6.01	4.96	73.3	5.93	5.47
Toluene	100	55.89	33.06	99.3	55.18	35.13
m,p-Xylene	100	54.95	33.45	99.3	53.08	31.88
o-Dichlorobenzene	0.7	1.75	1.34	0	1.64	0.51
o-Xylene	83	13.04	7.22	80.7	12.64	6.67
p-Dichlorobenzene	82.2	6.44	9.36	80	5.00	3.00

Because Pearson's correlation coefficient can be greatly affected by outliers and requires normal distributions of the variables, we used the Spearman's rank correlation coefficient, which does not use the actual observed data, but the ranks of the data, to compute a correlation coefficient. Table 3.16 shows Spearman's correlation coefficients between personal and indoor measurements. Statistically significant correlations were found for all the listed compounds.

Table 3.16. Spearman's correlation between indoor and personal exposures

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations:129

Indoor	Personal: p-Dichlorobenzene	Benzene	Chlorofom	Styrene	Tetrachloroethlylene	Toluene	m,p-xylene	o-xylene
p-Dichlorobenzene	**0.82478** <.0001	0.58583 <.0001	0.67337 <.0001	0.83602 <.0001	0.79371 <.0001	0.58856 <.0001	0.77981 <.0001	0.82715 <.0001
Benzene		**0.72594** <.0001	0.43814 <.0001	0.44400 <.0001	0.56285 <.0001	0.68167 <.0001	0.62505 <.0001	0.60445 <.0001
Clorofom			**0.91301**	0.79062 <.0001	0.71204 <.0001	0.41844 <.0001	0.64010 <.0001	0.68971 <.0001
Styrene				**0.87954** <.0001	0.81406 <.0001	0.59733 <.0001	0.75495 <.0001	0.80772 <.0001
Tetrachloroethlylene					**0.82299** <.0001	0.58228 <.0001	0.73544 <.0001	0.77759 <.0001
Toluene						**0.73845** <.0001	0.65226 <.0001	0.63953 <.0001
m,p-xylene							**0.82629** <.0001	0.83916 <.0001
o-xylene								**0.85957** <.0001

3.4.2. Outdoor measurements and indoor measurements

Outdoor/indoor ratio: The average outdoor concentration during the study period is summarized in Table 3.17. Among the target analytes, 1,1-dichloroethane, *o*-dichlorobenzene, *p*-dichlorobenzene, and chloroform were not (or almost not) detected in the outdoor air. The indoor/outdoor ratio for the rest of the target compounds were always greater than 1, indicating indoor sources for these compounds. The results are consistent with the findings by Lioy et al. (1991). In their study, three homes in the New Jersey area were assessed hourly for 12 hours; the indoor/outdoor ratio for benzene, styrene, toluene, *m,p*-xylene, and *o*-xylene were in the range of 2-3.

Table 3.17. Average outdoor concentrations and indoor/outdoor concentration ratio

	Percent Measurable	Mean(ng/L)	Std Dev.	Indoor/Outdoor Ratio
1,1-Dichloroethane	0	----	----	----
Benzene	100	5.78	2.44	2.18
Chloroform	1.2	0.49	----	----
Styrene	50	0.66	0.29	10.80
Tetrachloroethylene	98.8	3.38	1.82	1.75
Toluene	100	26.90	12.77	2.05
m,p-Xylene	100	26.40	13.59	2.01
o-Dichlorobenzene	0	----	----	----
o-Xylene	100	4.02	2.22	3.14
p-Dichlorobenzene	0	----	----	----

3.4.3. Personal VOC measurements and outdoor measurements

Table 3.18 shows Spearman's correlation coefficients between personal and outdoor measurements. Statistically significant correlations were found for tetrachloroethylene and *m,p*-xylene, but the correlation was small for *m,p*-xylene.

Table 3.18. Spearman's correlation between personal and outdoor concentrations

Outdoor	Benzene	Styrene	Tetrachloroethlylene	Toluene	m,p-xylene	o-xylene
Benzene	**-0.01796** 0.8399 129	-0.15617 0.0772 129	-0.15620 0.0771 129	-0.02444 0.7834 129	-0.11971 0.1766 129	-0.14899 0.0920 129
Styrene		**0.00866** 0.9433 70	0.00000 1.0000 70	0.07649 0.5291 70	0.03897 0.7488 70	0.05340 0.6606 70
Tetrachloroethlylene			**0.45065*** <.0001 129	0.22963 0.0088 129	0.36839 <.0001 129	0.40744 <.0001 129
Toluene				**0.13572** 0.1251 129	0.16878 0.0559 129	0.18660 0.0342 129
m,p-xylene					**0.17764*** 0.0440 129	0.19713 0.0251 129
o-xylene						**0.14774** 0.0948 129

3.4.4. Time-series analysis of the personal, indoor, and outdoor exposures, and time activities

Since only the 4 subjects in the subgroup were asked to collect personal and indoor badges, time-series analysis could only be conducted on the data from the subgroup. We first plotted the personal, indoor, and outdoor exposures for all the analytes (Figures 2a-2j). The purpose of the plotting is to determine whether we could average the measurements from the four subjects to build a common model (if the plots were similar) or to build one model for each subject and each chemical. Although the vertical axes vary from

subjects to subjects which made comparison less straightforward, it was obvious that different chemicals and subjects had different time trends.

Therefore, significant efforts were then made to fit the time-series model for each of the 10 chemicals for each of the 4 subjects (a total of 40 models). A forward stepwise method was used to select significant covariates from the 10 covariates (personal, indoor, outdoor, and 7 other sources). To illustrate the modeling process, we used the tetrachloroethylene exposure of subject 2473 as an example.

First, We started diagnosing the trend by examining the autocorrelation function of the indoor exposure measures. The autocorrelation function is a set of correlations of a time series observations paired with its own past values. An autocorrelated series cannot be analyzed with ordinary least squares regression and must be analyzed using time-series analysis techniques to adjust for the lack of independence of the autocorrelated errors. Table 3.19 is the output of the autocorrelation function up to lag 8. For example, the sample autocorrelation at lag 1, also called the sample autocorrelation of order 1, is related to the sample correlation of the time series against itself lagged by one day. The pattern of the autocorrelation function shown in Table 3.19 demonstrates that indoor exposures are autocorrelated up to lag 3. The chi-square test for white noise also indicates an autocorrelation.

Table 3.19. Autocorrelation check of indoor tetrachloroethylene exposure of subject 2473

Autocorrelations				
Lag	**Covariance**	**Correlation**	-1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1	**Std Error**
0	1974.785	1.00000	| |********** |	0
1	1577.842	0.79899	| . |********** |	0.176777
2	1326.280	0.67161	| . |********** |	0.266739
3	1078.416	0.54609	| . |********** . |	0.315183
4	752.070	0.38084	| . |******** . |	0.343481
5	539.408	0.27315	| . |***** . |	0.356432
6	428.100	0.21678	| . |**** . |	0.362915
7	270.342	0.13690	| . |*** . |	0.366939
8	72.364367	0.03664	| . |* . |	0.368531

"." marks two standard errors

Autocorrelation Check for White Noise									
To Lag	**Chi-Square**	**DF**	**Pr > ChiSq**	**Autocorrelations**					
6	60.56	6	<.0001	0.799	0.672	0.546	0.381	0.273	0.217

The exponential decay pattern of autocorrelation function of the indoor exposure indicated an autoregressive (AR) model. Therefore, we fitted the indoor exposures with an AR(1) model. When the model fits the data well, the residuals should distribute like white noise. The output in Table 3.20 indicates a good fit, confirmed by the residual check (Table 3.20).

Table 3.20. AR model for indoor tetrachloroethylene exposure of subject 2473.

Conditional Least Squares Estimation					
Parameter	**Estimate**	**Standard Error**	**T Value**	**Approx Pr > |t|**	**Lag**
AR1,1	0.97384	0.05320	18.30	<.0001	1

To Lag	**Chi-Square**	**DF**	**Pr > ChiSq**	**Autocorrelations**					
6	3.44	5	0.6325	-0.223	0.039	0.148	-0.113	-0.087	0.022
12	6.60	11	0.8305	0.091	0.095	-0.018	0.113	0.075	-0.163
18	10.74	17	0.8699	-0.059	0.071	-0.174	0.035	0.072	0.126
24	16.21	23	0.8462	-0.122	0.167	-0.050	-0.062	0.078	-0.046

Similarly, we checked the autocorrelation of the outdoor exposures (Table 3.21). The results indicate that the outdoor exposure was not autocorrelated, therefore, it was not necessary to fit the ARIMA model.

Table 3.21. Autocorrelation function of outdoor tetrachloroethylene exposure of subject 2473.

Autocorrelations				
Lag	**Covariance**	**Correlation**	-1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1	**Std Error**
0	34.252465	1.00000	| |**********|	0
1	7.670988	0.22395	| . |**** . |	0.176777
2	16.065275	0.46903	| . |********* |	0.185431
3	6.266316	0.18294	| . |**** . |	0.219394
4	3.716775	0.10851	| . |** . |	0.224111
5	3.412350	0.09962	| . |** . |	0.225747
6	-0.245527	-.00717	| . | . |	0.227116
7	0.710680	0.02075	| . | . |	0.227123
8	-0.195293	-.00570	| . | . |	0.227183

"." marks two standard errors

Autocorrelation Check for White Noise									
To Lag	**Chi-Square**	**DF**	**Pr > ChiSq**	**Autocorrelations**					
6	11.85	6	0.0653	0.224	0.469	0.183	0.109	0.100	-0.007

Next, personal and indoor exposures were pre-whitened to obtain a cross-correlation function (CCF) (Table 3.22). Personal exposure was also cross-correlated with the outdoor exposure to obtain the cross-correlation function (Table 3.23).

Table 3.22. Cross-correlation function (CCF) between personal and indoor tetrachloroethylene exposure of subject 2473.

Cross-correlations			
Lag	**Covariance**	**Correlation**	-1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1
-8	272.485	0.16129	| . |*** . |
-7	-411.295	-.24345	| . *****| . |
-6	469.712	0.27803	| . |******. |
-5	-334.272	-.19786	| . ****| . |
-4	53.997100	0.03196	| . |* . |
-3	-8.493743	-.00503	| . | . |
-2	118.480	0.07013	| . |* . |
-1	-260.638	-.15428	| . ***| . |
0	578.282	0.34229	| . |******* |
1	-112.793	-.06676	| . *| . |
2	243.259	0.14399	| . |*** . |
3	-306.272	-.18129	| . ****| . |
4	227.203	0.13449	| . |*** . |
5	15.905698	0.00941	| . | . |
6	-224.325	-.13278	| . ***| . |
7	72.713688	0.04304	| . |* . |
8	101.623	0.06015	| . |* . |

"." marks two standard errors

Table 3.23. Cross-correlation function (CCF) of personal and outdoor tetrachloroethylene exposure of subject 2473.

Lag	Covariance	Correlation	-1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1
-8	76.302289	0.21422	| . |**** . |
-7	0.070779	0.00020	| . | . |
-6	65.914771	0.18506	| . |**** . |
-5	46.241041	0.12982	| . |*** . |
-4	114.300	0.32090	| . |******. |
-3	90.357660	0.25368	| . |***** . |
-2	130.171	0.36545	| . |******* |
-1	104.863	0.29440	| . |******. |
0	180.528	0.50683	| . |********** |
1	172.087	0.48313	| . |********** |
2	120.901	0.33943	| . |******* |
3	163.396	0.45873	| . |********* |
4	22.358916	0.06277	| . |* . |
5	36.587342	0.10272	| . |** . |
6	45.637974	0.12813	| . |*** . |
7	-18.143280	-.05094	| . *| . |
8	-15.620875	-.04386	| . *| . |

The CCF indicated that the residual of personal exposure and indoor exposure was correlated without lags. The tail-off pattern of the CCF of personal exposure and outdoor exposure, however, suggested an AR factor in the transform function. We tried several models, and the best-fit and most parsimonious one was selected. Residual check indicated a good fit (Table 3.24).

Table 3.24. Fitting of the transfer model for tetrachloroethylene exposure of subject 2473. PE = personal exposure, IE = indoor exposure and OE = outdoor exposure.

Conditional Least Squares Estimation							
Parameter	**Estimate**	**Standard Error**	**t Value**	**Approx Pr > |t|**	**Lag**	**Variable**	**Shift**
AR1,1	-0.66213	0.19828	-3.34	0.0023	1	PE	0
SCALE1	0.68778	0.08317	8.27	<.0001	0	IE	0
SCALE2	5.30442	0.76577	6.93	<.0001	0	OE	0

Autocorrelation Check of Residuals									
To Lag	**Chi-Square**	**DF**	**Pr > ChiSq**	**Autocorrelations**					
6	8.64	5	0.1244	0.162	-0.011	-0.392	-0.017	0.097	0.194
12	11.63	11	0.3922	-0.099	-0.205	-0.041	0.033	0.087	-0.049
18	14.88	17	0.6038	0.035	-0.057	0.154	0.066	0.038	-0.117
24	18.87	23	0.7086	-0.049	-0.148	0.047	-0.060	-0.068	-0.068

Cross-correlation Check of Residuals with Input IE									
To Lag	**Chi-Square**	**DF**	**Pr > ChiSq**	**Cross-correlations**					
	3.29	5	0.6557	-0.103	0.017	-0.234	0.056	-0.038	0.180
11	5.45	11	0.9076	-0.054	0.061	0.008	-0.228	-0.064	-0.069
17	8.81	17	0.9460	-0.087	-0.025	0.034	0.223	0.184	0.110
23	17.00	23	0.8095	-0.148	-0.068	-0.115	0.457	0.083	-0.019

Finally, we added other exposure sources, such as a gas station, laundromat, etc., into the model. However, the effects were not statistically significant. The autoregressive factors, overall regression factor for indoor exposure and outdoor exposure for the final models are shown in Table 3.25. The final model is:

$$PE_t=0.69*PE_{t-1}+5.3*OE_t+\eta_t/(1-0.66B)$$

where B is the back shift operator; i.e. $BX_t=X_{t-1}$. After rearranging the equation, the model becomes

$$PE_t=-0.66PE_{t-1}+0.69*IE_t+0.45IE_{t-1}+5.3*OE_t+3.5*OE_{t-1}+\eta_t$$

Where PE = personal exposure, IE = indoor exposure and OE = outdoor exposure, at lag 0 (present day), PE_{t-1} = personal exposure, IE_{t-1} = indoor exposure and OE_{t-1} = outdoor exposure, at lag 1 (previous day), and η_t is the error term.

Table 3.25. Parameters for the final personal exposure model for tetrachloroethylene in subject 2473. There is no mean term in this model. IE = indoor exposure and OE = outdoor exposure.

Autoregressive Factors	
Factor 1:	1 + 0.66213 B**(1)

Input Number 1	
Input Variable	IE
Overall Regression Factor	0.687782

Input Number 2	
Input Variable	OE
Overall Regression Factor	5.30442

The general conclusion from this exemplary model for subject 2473 is that personal exposure to tetrachloroethylene was correlated with personal exposure yesterday, indoor exposures for today and yesterday, and with outdoor exposures for today and yesterday.

The above model fitting process was employed for each of the 4 subjects and each VOC. Four chemicals, 1,1-dichloroethane, chloroform, *o*-dichlorobenzene, and *p*-dichlorobenzene were not modeled because more than 50% of the measurements fell below the detection limit.

The results of the time-series analysis are summarized as follows:

1. Autocorrelation of the exposures:
Autocorrelation functions (ACF) were generated for all the chemicals for each subject. Statistical tests for autocorrelation were also performed. Table 3.26 lists the *p*-values for the chi-square test for detecting autocorrelation among the time series for the first 6 lags. The first 6 lags are autocorrelated if $p < 0.05$.

Table 3.26. P-value of chi-square test for detecting autocorrelation first 6 lags

	2469		2473		2474		2497		Outdoor Exposure
Chemicals	Indoor Exposure	Personal Exposure	Indoor Exposure	Personal Exposure	Personal Exposure	Indoor Exposure	Personal Exposure	Indoor Exposure	
Benzene (111)	<0.0001	0.0003	0.0330	0.0064	0.1482	0.2261	0.1213	0.0508	0.7569
Styrene(117)	<0.0001	0.0079	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Tetrachloroethylene(118)	0.0030	0.0017	<0.0001	<0.0001	<0.0001	0.0004	0.1920	0.5301	0.0863
Toluene (119)	0.0002	0.0004	0.0008	0.0822	0.0774	0.0651	0.0056	0.0039	0.5595
m,p-Xylene (122)	0.0003	0.0012	<0.0001	0.0010	0.0009	0.0177	0.0558	0.2994	0.7516
o-Xylene (123)	0.0014	0.0300	<0.0001	<0.0001	<0.0001	0.0012	0.1230	0.4499	0.6106

The results reveal the following:
a. Except for styrene, outdoor exposures were not autocorrelated. This suggests that during the study period, the air movement in the study area was strong enough to remove the residuals of the air concentrations of the previous day. This is important, because in places such as valleys where the outdoor exposure may not be carried away by air movement, the exposure will accumulate.

b. For subjects 2469, 2473, and 2474, almost all the indoor and personal exposures were autocorrelated, i.e., the measurements of a given day were correlated with measurements of the previous day. This suggests relatively stagnant air indoors as compared to outdoors.

Personal and indoor measurements for subject 2497, however, were not autocorrelated for most of the chemicals. This might be caused by better air exchange rate in this house. However, this speculation could not be confirmed by either the diary or baseline questionnaire. The baseline questionnaires indicated that all four homes opened doors and windows for about 10 hours each day. Furthermore, the home of 2497 did not appear to have significantly lower or higher exposure than other homes (Table 3.27). Worth noticing is the nearly identical personal and indoor values shown in Table 3.27. The activity diaries indicate that the subjects spent an average of 18 hours home, which may partially explain the close averages of indoor and personal exposures. In addition, some subjects might have left the personal badge home. Nonetheless, the plots of indoor and personal exposures showed that these two concentrations tracked each other, but were not identical. Figure 2d is the example of benzene for the four subjects. Except for subject 2469, who might have left the personal badge home on many days, the measurements of the rest of the three subjects indicated otherwise.

Table 3.27. Average indoor and personal exposure for each participant (unit: ng/L)

	Personal				Indoor			
Chemicals	2469	2473	2474	2497	2469	2473	2474	2497
Benzene (111)	0.98	1.12	1.01	1.02	0.98	1.12	1.01	1.01
Styrene(117)	5.82	6.64	5.98	6.02	5.81	6.63	6.00	6.00
Tetrachloroethylene(118)	1.71	1.96	1.76	1.78	1.71	1.95	1.77	1.77
Toluene (119)	5.52	6.30	5.68	5.72	5.52	6.30	5.70	5.70
m,p-Xylene (122)	1.62	1.85	1.67	1.68	1.62	1.85	1.68	1.68
o-Xylene (123)	5.42	6.18	5.57	5.61	5.42	6.18	5.59	5.59

2. Relationship between personal, indoor, and outdoor exposures:
We started the time series modeling by constructing ARIMA models for each subject and each chemical. The results, however, indicated that the same subject, rather than the same chemical, tended to have one general model format with variations in the parameters for each chemical. We then pooled the measurements of all the 4 subjects in the subset together to construct more general time series models using similar process described in 3.4.4.

The results indicate that the outdoor measurements were not correlated with personal exposures for most of the compounds. The outdoor concentrations of tetrachlorethylene and *m,p*-xylene of current day or previous day appear to correlate with current day personal measurements. The selected models for these two chemicals are:

PE_t=3.43+0.74OE_t (tetrachloroethylene)
PE_t=10.8+0.62PE_{t-1}+0.47OE_{t-1} (*m,p*-xylene)

3. Activities:
Seven exposure-related activities were examined, including the use of house-cleaning products: being at a gas station, being in a laundromat or hair salon, being near a smoker, painting and swimming. A forward stepwise method was used to incorporate the variables into the model. The models only indicated that being at a gas station was correlated with styrene, tetrachloroethylene, and *o*-xylene exposure for subject 2469; and styrene, tetrachloroethylene, toluene, *m,p*-xylene, and *o*-xylene exposure for subject 2474.

3.5. Breath VOC (Specific Aims 2.a & 2.d)

3.5.1. Descriptive statistics

Table 3.28 shows descriptive statistics for the VOC breath measurements for all 26 subjects including the two subjects who dropped out. More than 50% of the samples were below method-detection limit for four chemicals: 1,1-dichloroethane, carbon tetrachloride, chloroform, and o-dichlorobenzene.

Table 3.28. Descriptive statistics for breath VOC measurements

	Event and Baseline Combined (n=146)			Baseline (n=78)			Event (n=68)		
Chemicals	Percentage measurable	Mean (ng/L)	Std Dev	Percentage measurable	Mean (ng/L)	Std Dev	Percentage measurable	Mean (ng/L)	Std Dev
1,1-Dichloroethane	15	0.28	0	16.5	0.65	0	13.3	0.28	0
Benzene	96.6	2.14	2.49	94.9	1.89	1.57	98.5	2.41	3.22
Carbon tetrachloride	25.8	0.34	0.09	26.6	0.34	0.07	25	0.34	0.12
Chloroform	36.7	0.53	0.31	30.4	0.51	0.30	44.1	0.54	0.32
Methylene Chloride	89.1	2.80	4.23	84.8	2.98	5.11	94.1	2.60	3.12
Styrene	92.5	1.56	1.12	97.5	1.50	1.12	92.6	1.63	1.13
Tetrachloroethylene	97.3	4.11	9.64	98.7	4.73	9.99	95.6	3.48	9.28
Toluene	74.8	14.00	50.80	79.7	16.34	69.61	69.2	11.56	15.49
m, p-Xylene	96.6	4.40	5.92	98.7	4.42	6.38	94.1	4.38	5.43
o-Dichlorobenzene	4.8	0.45	0.04	8.9	0.45	0.05	0	0.45	0
o-Xylene	95.2	1.52	1.77	97.5	1.47	1.67	92.6	1.57	1.89
p-Dichlorobenzene	97.9	37.42	95.56	100	44.52	113.11	95.6	29.73	72.13

3.5.2. Breath/personal ratios

An interesting question for breath VOC is whether the VOCs in the breath samples came from the ambient air or were produced endogenously by the asthmatic children. We examined the ratio of breath VOC concentrations/outdoor concentrations and breath VOC concentrations/ personal concentrations. The results are shown in Table 3.29. The breath/personal ratios for all the chemicals were smaller than 1, with one exception. The values of the ratios were consistent with the findings in the TEAM study (Wallace et al., 1997). Results suggest that most VOCs were produced exogenously, and air was the predominant exposure pathway. It is interesting to note that the breath/personal ratio for *p*-

dichlorobenzene was greater than 1. Unlike other target VOCs, *p*-dichlorobenzene is widely used to control moths, molds, and mildew, and to deodorize. It exists in soap and also in foods such as pork, chicken, and eggs that are contaminated with *p*-dichlorobenzene from its use as an odor-control product in animal stalls. Therefore, in addition to air, *p*-dichlorobenzene has other exposure pathways, including dermal absorption and ingestion, which may be reflected in this study.

Table 3.29. Breath/personal ratio

Chemicals	Breath (n=146) Mean (ng/L)	Breath (n=146) Std Dev	Personal (n=4) Mean (ng/L)	Personal (n=4) Std Dev	Ratio Breath /Personal
1,1-Dichloroethane	0.28	0	1.67	0.52	0.17
Benzene	2.14	2.49	12.93	9.21	0.17
Carbon tetrachloride	0.34	0.09	3.17	2.88	0.11
Chloroform	0.53	0.31	----	----	----
Methylene Chloride	2.80	4.23	----	----	----
Styrene	1.56	1.12	7.26	2.68	0.21
Tetrachloroethylene	4.11	9.64	6.01	4.96	0.68
Toluene	14.00	50.80	55.89	33.06	0.25
m, p-Xylene	4.40	5.92	54.95	33.45	0.08
o-Dichlorobenzene	0.45	0.04	1.75	1.34	0.26
o-Xylene	1.52	1.77	13.04	7.22	0.12
p-Dichlorobenzene	37.42	95.56	6.44	9.36	5.81

3.5.3. Correlation between breath and outdoor VOC concentrations

Using pooled breath VOCs for the 24 subjects, we tested similar ARIMA modeling procedures described above. The results indicated that breath and outdoor VOC concentrations were not associated with each other for most of the compounds, except for benzene, styrene and *m,p*-xylene. The results indicated that breath VOCs (Y_t) were associated with lagged outdoor VOC measurements (lag 1 day or *t-1* and lag 2 days or *t-2*) as follows:

$Y_t=0.26Y_{t-1}+0.26OE_{t-2}$ (benzene)
$Y_t=1.24Y_{t-1}+0.23OE_{t-1} - 0.08OE_{t-2} + \eta_t - 0.88\ \eta_{t-1}$ (styrene)
$Y_t=0.28Y_{t-1}+0.09OE_{t-2}$ (*m,p*-xylene)

Recall that personal *m,p*-xylene was associated with lag 1 day outdoor *m,p*-xylene.

3.5.4. Within- and between-individual variance

The within- and between-individual variance of the breath VOCs are summarized in Table 3.30. Geometric standard deviations within individual ${}_g\sigma_W$, and between individual ${}_g\sigma_B$ were calculated for easier comparison. The results indicate that except for *p*-dichlorobenzene, within-individual variance was larger than between-individual variance. In occupational studies, this phenomenon is not uncommon. Our finding demonstrates that a longitudinal design study is necessary to investigate temporal exposure-response relationships that are expected to vary by individual.

Table 3.30. Within- and between-individual variations in breath VOCs

	$_l\sigma_W^2$	$_l\sigma_B^2$	$_g\sigma_W$	$_g\sigma_B$
o-Dichlorobenzene	1.10	0.11	2.99	1.12
p-Dichlorobenzene	1.22	1.31	3.39	3.70
Benzene	0.98	0.28	2.68	1.32
Carbon tetrachloride	0.83	0.17	2.29	1.18
Chloroform	1.07	0.29	2.91	1.33
Methylene Chloride	0.77	0.34	2.17	1.40
Styrene	0.84	0.49	2.32	1.64
Tetrachloroethylene	0.83	0.27	2.29	1.30
Toluene	1.02	0.48	2.79	1.62
m, p-Xylene	0.91	0.37	2.47	1.45
o-Xylene	0.98	0.27	2.66	1.31

3.6. Correlation between the chemicals

The Spearman's coefficients for personal exposure, indoor exposure, and breath VOCs are shown in Tables 3.31 to 3.33. The results show moderate to strong correlations for almost all the compounds in personal and indoor samples but weaker correlations between breath VOCs, except for benzene, toluene and xylene, which were strongly correlated in breath samples.

Table 3.31. Spearman correlation for personal VOCs

Spearman Correlation Coefficients, N = 129 Prob > |r| under H0: Rho=0						
	Benzene	Styrene	Tetrachloro-ethylene	Toluene	m,p-Xylene	o-Xylene
Benzene	1.00000	0.61069 <.0001	0.75168 <.0001	0.92342 <.0001	0.86183 <.0001	0.80571 <.0001
Styrene		1.00000	0.87367 <.0001	0.65428 <.0001	0.82810 <.0001	0.86998 <.0001
Tetrachloro-ethylene			1.00000	0.76229 <.0001	0.91652 <.0001	0.93566 <.0001
Toluene				1.00000	0.88712 <.0001	0.83446 <.0001
m,p-Xylene					1.00000	0.98572 <.0001
o-Xylene						1.00000

Table 3.32. Spearman correlation for indoor VOCs

Spearman Correlation Coefficients, N = 129
Prob > |r| under H0: Rho=0

	Benzene	Styrene	Tetrachloro-ethylene	Toluene	m,p-Xylene	o-Xylene
Benzene	1.00000	0.64974 <.0001	0.75185 <.0001	0.93572 <.0001	0.84237 <.0001	0.80255 <.0001
Styrene		1.00000	0.87712 <.0001	0.69950 <.0001	0.86811 <.0001	0.89575 <.0001
Tetrachloro-ethylene			1.00000	0.77393 <.0001	0.90708 <.0001	0.92017 <.0001
Toluene				1.00000	0.87675 <.0001	0.84117 <.0001
m,p-Xylene					1.00000	0.98927 <.0001
o-Xylene						1.00000

Table 3.33. Spearman correlation for breath VOCs

Spearman Correlation Coefficients, N = 141 Prob > |r| under H0: Rho=0

	Benzene	Styrene	Tetrachloro-ethylene	Toluene	m,p-Xylene	o-Xylene	p-Dichloro-benzene
Benzene	1.00000	0.23880 0.0043	0.44676 <.0001	0.68448 <.0001	0.65011 <.0001	0.61257 <.0001	0.23035 0.0060
Styrene		1.00000	0.00842 0.9210	0.38036 <.0001	0.49703 <.0001	0.56304 <.0001	0.10798 0.2025
Tetrachloro-ethylene			1.00000	0.24657 0.0032	0.31161 0.0002	0.27936 0.0008	0.26644 0.0014
Toluene				1.00000	0.70157 <.0001	0.67476 <.0001	0.20147 0.0166
m,p-Xylene					1.00000	0.94120 <.0001	0.26253 0.0017
o-Xylene						1.00000	0.25930 0.0019
p-Dichloro-benzene							1.00000

4. RESULTS OF THE EPIDEMIOLOGICAL STUDY

4.1. Overview of Epidemiological Results

Results for the analysis of epidemiological data will be presented as follows:

1) an assessment of diary data quality for all days of follow-up along with detailed descriptions of individual subject data (Section 4.2.), this includes an assessment of diary (symptom score) versus canister classification (event versus baseline) (Section 4.2.5.);
2) descriptive data on outcomes and exposures for breath canister days (Sections 4.3.1. to 4.3.2.) followed by a preliminary regression analysis of asthma symptoms and exhaled breath VOC data to determine binary cut-off points, control variables, and the influence of potentially unreliable diary data determined in sections under number 1 above (Section 4.3.3);
3) analyses of health effects of breath VOC as compared with ambient VOC exposures (Sections 4.3.4. to 4.3.5.), this includes analyses of health effects of ambient criteria air pollutant gas exposures for breath canister days;
4) descriptive data on outcomes for personal badge VOC days among the four volunteers in the exposure assessment study, followed by analyses of health effects of personal VOC exposures (Section 4.4);
5) descriptive data on outcomes and ambient exposures for all days of the panel study (Sections 4.5.1. and 4.5.2.), followed by analyses of health effects of ambient exposures, including daily VOCs, criteria air pollutants, and elemental and organic carbon fractions of PM_{10} (Sections 4.5.3. to 4.5.5.).

4.2. Epidemiological Data Quality and Descriptive Subject Data

4.2.1. Approach to Determining Data Quality: We determined a plan of action from a detailed problems list concerning asthma diaries for 26 participants that was discussed with RLANRC staff. Table 4.1 summarizes this initial approach to coding flags, and is not comprehensive with respect to the final flag coding. The final coding scheme for flags is shown in Table 4.2. Flag coding was applied to the diary data during keypunching by QA staff and by data processing in SAS. As discussed previously, two subjects were excluded from further study due to noncompliance (ID 2471 and 2493) leaving the total sample at 24 subjects for the epidemiologic analysis, which was the target sample size. Our assessment of the diary data shows that several of the other subjects had difficulty with proper diary completion despite retraining. Their data was extensively flagged as discussed below.

Table 4.1. Initial examples of asthma diary problems and coding actions, Asthma Panel Study, Huntington Park region (Oct 21, 1999 - Jan 23, 2000, all days including run-in with no ambient exposure data up to Nov 4, 1999)

ID	Problems & Questions / UCI	Answers / LAREI	Coding Action
2468	Highest symptom severity was blank to 1/10 and 1/17-1/22.	Our mistake in overlooking this. See 2nd comment below.	See below
	Subject was asymptomatic before Jan., why continued?	Subject did have symptoms in December, and was good about providing canisters.	N/A
	Unclear if symptom severity blank, should we code day's highest symptom severity 0 if the four times are 0.	Otherwise, we infer that the subject intended a blank highest symptom severity to mean zero when all times are zero.	Code sxsevere = 9999 Sx_Flag = 9
	On 1/23 see a severity of 3 but all times are 0.	We cannot explain the 3.	Code sxsevere = 3 Sx_Flag = 6
2469	10/21-23 daily Rx med unclear	Albuterol	Code an rxmed1 Albuterol
	Azmacort is not an as-needed med, should it have been albuterol?	In the instance in question, we believe he did take Azmacort. Otherwise, Albuterol was the as-needed med. See comment C below.	Code Rx_flag = 2 each day of Azmacort use
2470	Two diaries are marked the week of 11/15. One marked 11/15/99 has duplicate data marked 11/22 and both have only the first day's symptom question coded.	My best guess is that the "11/15" with only one day's data actually represents 12/20. On 11/22 sheet, I believe the blanks all represent zero symptoms. -Mari	Do not code duplicate data.
2471	We will not be coding this subject — noncompliant, asymptomatic	We concur. Note: Subject appeared to be a good performer and did report symptoms in the pilot study.	Do not code
2472	OK		
2473	Assume no meds taken despite 0 marks.	Correct, based on our review.	Code no med variables (make blank)

Table 4.1. (continued)

ID	Problems & Questions / UCI	Answers / LAREI	Coding Action
2474	Looks like one-week recall throughout (see same color marks, etc.), may drop subject from analysis.	We recommend keeping this subject. See comments A, B below.	S x_flag=7 all days
	12/27-1/2, suspicious white out on all days across asthma symptom severity with note "I thought it said headache." Suggests diary is filled out at end of week.	Not necessarily. I found this subject to be bright and cooperative, and believe her reports are valid. I think she mistakenly put headache data in the asthma symptom severity spaces, then wrote the note and made the white-out corrections. –Mari	See above
	Rx med too consistent.	See above; see comment B below.	Code as is
2483	OK		
2484	Unclear what as-needed inhalers are, and they do not correspond to symptoms.	Albuterol. Also was on prednisone during December, but not prior to study, according to his reports.	Code prnmdi1 as Albuterol
	No correspondence between symptom severity and time of highest severity EVER!	We agree that reports are unreliable; we cannot reconstruct his actual symptom or medication experience.	Use appropriate Sx_flags
	School inhaler was given on days with symptom score=0.		Code as is
2485	Appears a ventolin inhaler was available but not coded until used on 12/16-18	We believe she did have ventolin available but did not use it because of mild or no symptoms before 12/16.	Code prnmdi1 = 9999 before 12/16; Rx_flag = 3
	Extreme variation in Resp Infections.	See comments B, D below.	Code as is; Sx_flag =11 for all days
2486	Numbers are circled in many places, is this a change to zero?	Yes, the subject made the changes to zero.	Code as zero; Where appropriate: Sx_Flag = 5 Rx_flag = 4 Sx_flag =10
	Ventolin inhaler marked only when used, no zeros (note, we would code the inhaler as missing rather than zero).	We believe that the inhaler used was always Ventolin, and that blanks indicate zero uses.	Code prnmdi1 = 9999 if blank; Rx_flag = 3
	Curious pen marks – red for PEF, another color for rest. Know why?	Can't tell from Xerox copy.	Code as is

Table 4.1. (continued)

ID	Problems & Questions / UCI	Answers / LAREI	Coding Action
2487	Looks like numbers are made up, filled out at end of week, may drop.	Possible. This subject seemed promising at the beginning, but later complained that the study interfered with her schoolwork (according to report from father) and was difficult to keep motivated. -Mari	SX_flag = 7 throughout
	Mari marked symptom=0 per subject for week, but see as-needed inhalers were used, and there was a week with a resp. infection. Code all missing?	Child left blanks; I questioned her; she said she takes all her meds with or without symptoms. I wrote what she told me. –Mari	Leave prnmdi blank Code inhalers as rxmeds Rx_flag = 1 all days
2488	Poor compliance throughout.	We disagree. Subject appeared to do well with canisters, activity diaries, peak flows. Tends to give low numbers for symptom severity, but positive entries seem to coincide with low peak flows.	Be careful, use flags.
	Missing symptoms are=0?	Yes; I confirmed that with the subject, as noted on forms. –Mari	Code sxsevere = 9999 Sx_Flag = 9 or 2 where appropriate
	Subject says "was in the Doctor." What for?	Don't know; probably not for acute asthma, given lack of symptoms.	Ignore
2489	Extreme variation in Respiratory Infections.	See comments B, D below.	Code as is; Sx_flag =11 for all days
2490	11/25 &11/26 line crosses through data. What for?	Don't know; can't find our copies for these dates; possibly intended to flag them as holidays. (When convenient, we would appreciate it if you would send us copies of the asthma symptom diaries for the 2 weeks beginning 11/15.)	Code missing
	As-needed inhaler noted later on 12/6 – same at beginning?	Yes, we think so.	Code prnmdi1 before 12/6;
2491	Numerous days with missing symptom code, even extended period.	As indicated in my notes on diaries, I confirmed with the subject that blanks indicate zero symptoms. –Mari	Code sxsevere = 9999 Sx_Flag = 2 or 9 as appropriate
	Same color pen/pencil on entire sheets – possible 1-week recall.	See comment A below.	S x_flag=7 appropriate weeks

Table 4.1. (continued)

ID	Problems & Questions / UCI	Answers / LAREI	Coding Action
2492	Odd PEF numbers not in 10s or 5s. Was the subject retrained?	No. We suspect that what look like sixes are zeros.	Round PEF numbers to 10s
	Same colored pen last 6 weeks – suggests 1-wk recall.	See comment A below.	S x_flag=7 appropriate weeks
	Was prednisolone that was started 11./28 taken until 12/2?	Yes, we believe so.	Code rxmed prednisolone for 11./28 until 12/2
2493	Noncompliant – will not code.	Agree. Subject was dropped in early weeks.	Do not code
2494	Poor compliance, very unclear asthma coding.	Circled numbers are the correct total inhaler puffs per day. Note that subject continued to record data beyond cutoff date of Dec. 20.	Use flags prnmdi1 = circled total
	Assume only 1 as-needed inhaler from start is Albuterol?	Yes, albuterol.	Code only prnmdi1
2495	Assume only 1 as-needed inhaler from start is Albuterol?	Yes, albuterol.	Code only prnmdi1
2496	OK		
2497	Assume only 1 as-needed inhaler from start is Proventil?	Yes, Proventil.	Code only prnmdi1
	No notes on hospitalization. Was it for asthma? If so, the symptom severity is 5 for days in hospital.	Yes, hospitalized for asthma, severity should be 5 for entire week.	Code sxsevere = 5 all that week.
2498	Assume 2 as-needed inhalers used from start, not 3, Albuterol and Ventolin? All zero, no symptoms.	Correct.	Code only prnmdi1 and prnmdi2 All zero
2499	Assume only 1 as-needed inhaler from start is Ventolin?	Correct.	Code only prnmdi1

Table 4.1. (continued)

ID	Problems & Questions / UCI	Answers / LAREI	Coding Action
2500	No as-needed beta-agonist inhalers.	Correct.	No prnmdi coded
	Assume Vanceril, Theo and Singulair are Rx meds, not as-needed.	Correct.	Code rxmed1 to 3 and Dlyrx 1 to 3
	Amoxicillin started on 11/15, no notes and no "yes" responses for respiratory infection	We don't know what the amoxicillin was for; apparently not a respiratory infection, given the report of no respiratory symptoms.	Do not code amoxicillin Code Respiratory Infection as is
2501	Meds unknown for first 4 weeks.	We believe the med used was Azmacort.	Code as rxmed1 = Azmacort
	Azmacort on 12/13, not as-needed.	See comment C below.	Code as rxmed1
	Ventolin appears to be used as maintenance med, not as-needed (symptoms were zero).	Correct. See comment C below.	Code as rxmed2
	Albuterol nebulizer is only as-needed?	Yes.	Code as prnmdi1
	Extreme variation in Resp Infections.	See comments B, D below.	Sx_flag =11 for all days

COMMENTS FROM LAREI, ANSWERS FROM R DELFINO, UCI:

Comment A: A whole week's data in the same color ink may raise suspicion, but should not automatically imply that the subject made all entries at the end of the week. A subject may leave one pen in the bag with other materials and use it consistently. Our feeling is that reported data should be taken as valid, in the absence of strong evidence to the contrary.

Answer/RD: The approach used is one that can be applied in a sensitivity analysis in which data are included then excluded. The approach described is that used by Anne Woolcock and others who have been doing asthma panel studies with paper diaries for many years.

Comment B: Too much consistency over time is stated as a reason to reject data in some instances. In others, too little consistency is stated as a reason to reject. This is reasonable in principle, but shouldn't there be clear written criteria for a "credible degree of consistency over time", which would have to be violated before data are thrown out? If there are no such criteria, then to our way of thinking, we should accept subjects' reports at face value, unless they are self-contradictory.

Answer/RD: ditto the above. A subject's report cannot be taken at face value given our expectation that falsification of diary records is common, but difficult to objectively "prove."

Comment C: As pointed out in previous discussions and reports, we have reason to believe that many of these subjects use non-standard asthma treatments and/or use standard medications in ways inconsistent with the packaged instructions. Again, we believe that when in doubt, reports should be taken at face value, even if they suggest unconventional and inappropriate asthma management.

Answer/RD: ditto the above. But, we can, as in the past (Delfino et al., EHP 1997), code anti-inflammatory meds to as-needed where they are used inappropriately as such – i.e., the reports are useful as an indicator of asthma exacerbations. Note: this was not done, i.e., all coded as-needed inhaler use were beta-agonists.

Comment D: Symptoms of upper respiratory allergy and upper respiratory infection are not mutually exclusive, either in real life or in the symptom diary instructions. In the cases we reviewed, reported infectious symptoms were implausible because they came and went too quickly, suggesting that they were really allergic symptoms. Would it be reasonable to pool infectious and allergic symptoms to test their relationship with asthma and/or exposures?

Answer/RD: No, respiratory infections and allergic symptoms can confound or modify air pollution effects in different ways.

Table 4.2. Flag codes for the Asthma Diary, Asthma Panel Study, Huntington Park region.

PEFR Flags (variable PF_Flag):

1 = All 3 PM PEFR exactly the same
2 = High outlier (>3 IQR above 3rd quartile of the session maximum PEF), may be valid – check univariate
3 = All 3 AM PEFR exactly the same
4 = Low outlier (>3 IQR below 1st quartile of the session maximum PEF), may be valid – check univariate and symptoms, MDI
5 = number not readable (code data 8888)
6 = greater than 10% difference between the highest and 2nd highest PEF maneuvers
7 = 2 days of data have exactly the same values
8 = All PEFRs are the same showing odd multi-day pattern
9 = 3 AM PEFR = 3 PM PEFR in exact number sequence.
10 = Odd numbers for PM PEFR (meter division marks are by 10 L/min)
30 = Odd numbers for AM PEFR

Flags for Symptom Score, Time of Greatest Severity, Headache, Respiratory Infections and Allergy (variable Sx_Flag):

1 = symptom score>0 entered, but no time of severity
2 = no symptom score, but time of severity entered
3 = symptom score of 0 entered, but time of severity entered
4 = >1 time of severity, used first time entered or first time with same symptom score number: subject is still doing numbers not check marks
5 = suspicious entry, number changed
6 = suspicious entry, time of severity coded all zeros
7 = penmark same all week;
8 = awakened at night but sxsevere=0.
9 = missing symptom score not coded 0 despite report of no symptoms
10 = suspicious entry for headache severity, number changed
11 = extreme variation in respiratory infections

Flags for MDI and Daily Rx Meds (variable Rx_flag):

1 = subject entry for prn mdi no. 1 is an anti-inflamatory med used as-needed
2 = subject entry for prn mdi no. 2 is an anti-inflamatory med used as-needed
3 = no use of as-needed inhaler was left blank instead of coded as a 0
4 = suspicious entry, number changed
5 = daily Rx medication (RXMED) coded under as-needed but used regularly rather than as-needed.

***4.2.2. Subject-specific descriptive data*:** Table 4.3 shows descriptive data for the individual subjects. There were 5 females and 19 males, which is somewhat higher than the usual 2:1 male to female ratio. All but one subject, an American Indian, identified himself or herself as Hispanic. Four subjects were in the exposure assessment study. Eleven subjects were in the extended study through the month of January. Several subjects had low overall average symptom scores and no as-needed inhaler use suggesting they had very mild asthma (discussed in Section 4.5.1. below). Table 4.4 shows the socioeconomic status (SES) of families as reported by parents. Three families refused to give any of this information and some stated the specific SES level was unknown. Overall, the data indicate a low SES for the panel as expected for the region of study.

Table 4.3. Characteristics of individual subjects in the Asthma Panel Study, Huntington Park region, Oct 21, 1999 to Jan 23, 2000.

ID #	Age	Sex	Race[a]	Ht	Entry Date(s)	End Date(s)	Study Status[b]	Mean Daily Symptom Score (SD)	Mean As-needed Inhaler (SD)[d]	Anti-inflammatory Medication[e]	Mean Morning PEFR (L/Min) (SD) min/max	Mean Evening PEFR (L/Min) (SD) min/max	Grade & School[g]
2468	11	M	3	60	10/28/99	01/23/00	1, 2	0.10 (0.50)	6.00 (0.00)		378 (18) 350/400	378 (17) 300/400	6 (1)
2469	10	M	3	55	10/21/99	01/23/00	1, 2, 3	0.51 (0.99)	2.33 (1.86)		251 (44) 190/360	254 (44) 190/350	5 (3)
2470	16	M	3	65	11/01/99	12/20/99	1	0.00 (0.00)	0.10 (0.65)		448 (45) 330/500	479 (52) 320/640	8 (2)
2472	11	M	3	54	10/28/99	01/21/00	1, 2	0.16 (0.44)	0.65 (1.84)	Becl/Pl[h]	267 (35) 120/360	269 (32) 130/320	6 (1)
2473	14	M	3	66	10/29/99	12/12/99	1, 3	0.02 (0.15)	0.00 (0.00)		389 (32) 320/490	381 (29) 310/450	9 (4)
2474	11	F	3	59	10/28/99	01/23/00	1, 2, 3	1.06 (0.82)	1.29 (1.08)	Flut	316 (27) 280/500	313 (17) 290/390	6 (1)
2483	13	M	3	55	10/27/99	01/23/00	1, 2	0.14 (0.38)	1.50 (0.71)		370 (37) 300/420	370 (42) 260/420	7 (2)
2484	11	M	3	60	10/26/99	12/20/99	1	0.49 (0.62)	--		313 (35) 240/380	367 (55) 270/470	6 (1)
2485	16	F	3	74	10/26/99	12/19/99	1	0.58 (0.74)	2.00 (1.63)		394 (34) 280/450	403 (28) 310/450	9 (8)
2486	11	F	3	65	10/26/99	12/19/99	1	0.26 (0.44)	2.00 (0.00)		380 (23) 340/440	419 (20) 390/490	6 (2)
2487	12	F	3	58	10/25/99	12/19/99	1	0.94 (1.23)	0.00 (0.00)		512 (46) 410/560	510 (46) 420/560	7 (2)
2488	15	M	3	66	10/26/99	01/23/00	1, 2	0.37 (0.75)	0.60 (1.14)	Becl	410 (82) 230/550	452 (80) 290/600	9 (5)
2489	13	M	3	66	11/02/99	12/17/99	1	0.04 (0.30)	0.00 (0.00)		360 (57) 250/550	370 (56) 250/490	8 (1)
2490	12	M	3	65	11/12/99	01/23/00	1, 2	0.33 (0.71)	1.38 (1.93)	M	283 (48) 160/400	317 (52) 200/470	7 (6)
2491	11	M	3	61	10/27/99	01/23/00	1, 2	0.57 (0.71)	0.88 (1.30)		364 (73) 190/500	375 (73) 160/510	6 (2)
2492	12	M	3	61	10/28/99	12/19/99	1	0.15 (0.42)	0.00 (0.00)	Pl[h]	385 (18) 320/410	386 (16) 350/410	7 (2)
2494	11	M	3	52	10/28/99	12/22/99	1	0.22 (0.51)	3.59 (0.54)		277 (43) 200/350	277 (50) 220/420	5 (7)
2495	14	M	6	64	10/28/99	12/19/99	1	0.06 (0.32)	0.05 (0.30)		365 (46) 210/410	376 (18) 320/400	9 (5)
2496	13	F	3	65	10/28/99	01/23/00	1, 2	0.09 (0.36)	0.00 (0.00)	Becl prn	386 (12) 360/420	387 (13) 350/420	8 (2)
2497	13	M	3	58	10/29/99	01/24/00	1, 2, 3	1.09 (1.72)	2.83 (1.71)		201 (32) 130/300	206 (30) 140/300	8 (1)
2498	11	M	3	56	11/15/99	12/19/99	1	0.00 (0.00)	0.00 (0.00)		216 (26) 180/280	230 (23) 200/290	6 (2)
2499	10	M	3	57	10/29/99	12/19/99	1	0.00 (0.00)	0.00 (0.00)		232 (20) 180/290	228 (21) 170/280	5 (7)
2500	14	M	3	63	10/29/99	12/21/99	1	0.11 (0.37)	0.00 (0.00)	Becl/M	301 (29) 250/390	313 (35) 230/380	8 (1)
2501	12	M	3	62	11/15/99	01/22/00	1, 2	0.48 (0.98)	3.00 (0.00)	Becl/TriAc/ Pd[h]	333 (30) 210/400	338 (13) 310/400	6 (1)

[a] 1 = White, non-Hispanic; 2 = Black; 3 = Hispanic; 4 = Asian, Pacific Islander; 6= American Indian/Alaskan native.

[b] 1= participation in initial panel period (Nov-Dec, 1999); 2= additional participation in extended panel period (Jan, 2000); 3= in exposure assessment trial.

[c] Subjects 2473 and 2495 had no symptoms during the period after October when exposures were measured.

[d] Average daily number of puffs of β-agonist metered dose inhalers.

[e] Antiinflammatory Medications: TriAc – Triamcinolone Acetonide; Becl - Beclomethasone dipropionate; M – Montelukast; Pd – Prednisone; Pl – Prednisolone; Flut – Fluticasone propionate;

[f] FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; Early: tested in the first 3 weeks; Late: tested at the end of study.

[g] Schools: (1) Henry T. Gage middle school; (2) Chester W. Nimitz middle school; (3) Nueva Vista magnet; (4) Bell high school; (5) Huntington Park high school; (6) Fishbone Avenue middle school; (7) San Antonio elementary; (8) Harbor Occupational center.

[h] Subject took prednisolone or prednisone for a few days during a respiratory infection.

Note: β-agonist preventive medications were also taken -- 2474 took Salmeterol Xinaofoate and oral Theophyllin; 2497 took Salbutamol; 2500 took oral Theophyllin

Table 4.4. Socioeconomic status, Asthma Panel Study, Huntington Park region

ID	Maternal Education Level[a]	Paternal Education Level[a]	Occupation Level of Maternal Parent[b]	Occupation Level of Paternal Parent[b]	Family Income Level[c]
2468	1	1	2		
2469	1	1	2	3	2
2470	2	2	2	2	2
2472	1	1	2		1
2473	6	6	1		3
2474	4	3			4
2483	2	2	2	3	2
2484					
2485	2	1	2	1	1
2486	2	1	2	1	1
2487	1	2	2	1	1
2488	2	1	2	6	1
2489	4		2		1
2490	2		2		1
2491	1	1	2	2	6
2492	1	1	2	3	3
2494	2	2			2
2495			2		1
2496					
2497	2	1	6	6	
2498	2	7		6	2
2499	2	1			6
2500					
2501	4	2	2	3	2

[a] Education Level: 1 = Elementary K – 8; 2 = High School; 3 = Trade, Technical or Business School; 4 = Community College (2 years); 5 = Undergraduate College (4 years); 6 = Professional or Graduate School; 7 = Unknown.

[b] Occupation Level: 1 = Unemployed; 2 = Housewife / Househusband; 3 = Blue Collar Worker; 4 = White Collar Worker; 5 = Professional; 6 = Unknown.

[c] Income Level: 1= Less than $15,000; 2 = $15,000 to $29,999; 3 = $30,000 to $49,999; 4 = $50,000 to $ 75,000; 5 = More than $75,000; 6 = Unknown.

4.2.3. PEF Data Quality: Table 4.5 shows the frequency of PEF flags (PF_flag) and other problems for PEF maneuvers by individual subjects. When all three repeated PEF measurements are exactly the same either for one test session or across several days (PEF flags 1, 3, 7 & 8), there is a possibility that all or some of the maneuvers were not done and data were entered falsely or incorrectly. Replication of PEF for all three maneuvers may actually occur on occasion, but our suspicion increases when the phenomenon occurs repeatedly. These flags indicate a serious concern with PEF data for ID no's 2484 and 2487. Other subjects follow in decreasing severity of this potential problem: 2469, 2501, 2488, 2468, 2474, 2490 and 2498. The rest of the data flagged as such are of little concern.

Table 4.5. Session counts for problems with peak expiratory flow rate data by individual subjects: Asthma Panel Study, Huntington Park region, Oct 21, 1999 to Jan 23, 2000

ID	All 3 Evening (PM) PEF Same (PF_Flag=1)	All 3 Morning (AM) PEF Same (PF_Flag=3)	Multiple Days with Same PEF pattern (PF_Flags= 7 & 8)	Identical Sequence of AM & PM PEF Values (PF_Flag=9)	Odd PM PEF Values (PF_Flag= 10)	Odd AM PEF Values (PF_Flag= 30)	>10 % Difference Between the Highest and 2nd Highest PEF: AM (%) & PM (%) (PF_Flag=6)	High Max PEF Outliers (PF_Flag=2)	Low Max PEF Outliers (PF_Flag=4)	Missing PEF Data	Total AM & PM Obs.
2468	2		5	4			19 (26); 21 (28)		1	1	148
2469	11	7		1			15 (19); 10 (13)			8	154
2470	3	3					2 (5); 8 (18)				88
2472	2	2		1			5 (6); 7 (9)	2	7	4	158
2473		1					3 (7); 3 (7)			1	90
2474	6	4		6			4 (5); 2 (2)	3		6	162
2483	2	1		2			12 (16); 11 (15)			4	150
2484	15	17	40		16	14	0 (0); 3 (6)			3	94
2485		1		1			4 (7); 3 (5)		4	3	110
2486		1					7 (13); 2 (4)	5		1	110
2487	24	20	7	10	15	12	1 (2); 0 (0)		23	2	106
2488	7	7		4			8 (10); 5 (6)			12	168
2489	1				1		23 (50); 18 (39)			1	92
2490	4	3		2			19 (30); 11 (17)			5	128
2491	1	2					47 (57); 48 (58)			3	166
2492							10 (19); 4 (8)		1		106
2494	1						22 (45); 20 (41)			3	98
2495							19 (40); 27 (56)		3		96
2496		2		1			2 (2); 0 (0)	1		2	162
2497		1		11			21 (26); 20 (25)	4	1	1	160
2498	3	3					8 (23); 9 (26)			1	70
2499	1						8 (21); 14 (36)				78
2500	1	1					6 (11); 7 (13)	2		2	108
2501	5	10		4			2 (3); 2 (3)	3	3	3	128
Total	89	86	52	47	32	26	267 (18); 255 (17)			66	2930

We found some instances where the 3 morning PEF and 3 evening PEF maneuvers were in an exactly equivalent number sequence (PF_flag 9), e.g., 200, 210 220. Two subjects showed this pattern on 10 and 11 sessions, and one was 2487 noted above as also having all 3 session maneuvers identical in 44 sessions. Odd PEF values that cannot be reasonably read off the meter (e.g. 221, 236, 247 rather than 220, 240, 250) were frequently found in 2 subjects, ID 2484 and 2487. Recall that these were 2 of 3 subjects above with numerous duplicated PEF values. All odd values were later rounded to the standard 10 L/min, which is the limit of resolution for reading the meters (this is included in training).

Another potential problem is when maneuvers are frequently far apart from each other, suggesting that the subject had difficulties doing forced expiratory maneuvers. We assessed this by examining the difference between the largest and second largest PEF within a test session. An acceptable target for PEF reproducibility within a test session has been determined by an expert panel to be a difference of 10% or less (Cherniack et al., 1992). We therefore examined the frequency of > 10% reproducibility by each subject. Normally to achieve the 10% rate, more maneuvers are allowed until the subject reaches that goal, but we chose to follow the usual panel study approach of 3 maneuvers to avoid overburdening subjects. We found that > 10% PEF difference occurred on 17.8% of all morning and evening PEF test sessions. Table 4.5 shows that 9 subjects had trouble with achieving good reproducibility with over 20% of either their morning or evening PEF data not reaching the 10% target. An alternate choice would have been to instruct subjects to perform more than 3 maneuvers if the difference between 2 maneuvers is more than two divisions on the meter, or 20 L/min (Enright et al., 1995). The distribution of PEF differences >10 L/min is shown in Figures 3a and 3b. Subjects with frequently large differences over 30 L/min on >20% of AM or PM test sessions included: 2468, 2470, 2483, 2489, 2490, 2491, 2492, 2494, 2495, and 2498. Note that the two subjects flagged with the highest frequency of 3 identical maneuvers noted above (2484, 2487) were not in this group and had nearly perfect reproducibility. Maneuver-induced bronchospasm may explain some of the PEF differences, but the larger differences should be infrequent in well-trained subjects performing the test properly (Enright et al., 1995).

Table 4.5 also shows data for PEF flags 2 and 4, or high outliers, defined as a session maximum PEF over 3 times the interquartile range (IQR) above the 3rd quartile, and low outliers, defined as a session maximum PEF more than 3 IQR below the 1st quartile. The IQR were often small and so low statistical outliers were likely within lower PEFs expected during bronchoconstriction. Subject 2487 who had the most frequent low outliers, also had the highest average PEF (Table 4.3) and the low values for morning and evening were 460, which is not an unexpected decrease from the subject's PEF means of 512 and 510, respectively. None of the subject outliers (including minimums and maximums, Table 4.3) were unexpected

There were 27 PEF entries that were invalidated because they were illegible (PEF flag 5, not shown in Table 4.5). However, in all of these cases the other two maneuvers in the test session were legible.

After excluding days with no diary entries at all, the amount of missing PEF data was unexpectedly low (2.2%). Our recent asthma panel study employing electronic diaries and electronic FEV_1 meters showed no diary entries on 10% of expected times and no FEV_1 on 12% of expected times, both confirmed with time-date stamps (Delfino et al., 2001a; 2001c). The lower proportion of missing data in the present study should be viewed in light of the high reproducibility (identical maneuvers) among two subjects. Some falsification of data is to be expected when people have to write down the values and don't believe anyone is checking.

4.2.4. Symptom Data Quality: Table 4.6 shows the frequency of flags and other problems by individual subjects for other health outcomes that were entered into the daily diary. For asthma symptoms, the diary included both the asthma symptom severity question, and a set of responses for the subject to indicate

when their asthma was at its greatest severity if and only if they had any asthma that day (see attached diaries in English and Spanish). Therefore, if the asthma symptom score was 0 (no symptoms), then the subject should not have answered this later question on time of greatest asthma severity. Also, if they had no asthma symptoms, they were instructed to enter an asthma symptom score of 0 rather than leaving the field blank. Many subjects had difficulty understanding these instructions despite repeated retraining at the weekly home visits. These problems are indicated in symptom flag (Sxflag) codes 2, 3 and 9. Symptom flag 2 indicated that the subject left the symptom score blank but the time of severity was entered. For these instances, symptom data were left missing because it was not possible to determine the level of asthma symptom severity. This was a frequent problem with only 2 subjects: 2490 and 2491. Symptom flag 3 indicated that the subjects coded the symptom score as 0, but entered a time of severity. For these instances, we left the code 0 because we believe the subjects understood the single question about asthma symptoms, but the time of severity question confused them. Most subjects understood what to do here and some were confused only at first or intermittently made mistakes. In 3 others, despite retraining, this was a persistent problem: IDs 2490, 2494 and 2495. Several subjects failed repeatedly to put an asthma score of 0 when they later reported they had no symptoms at the weekly follow-up (Table 4.6, symptom flag 9). The symptom data were left missing in this case to prevent the use of inaccurately recalled symptoms.

Subjects were instructed that for the scoring of asthma symptoms, if they were awaked at night because of asthma, then they should put down an asthma severity score that represented the severity of the nocturnal asthma. Out of 170 reports of nocturnal asthma, subjects failed in 91 instances to also record a consistent asthma severity score (16 missing symptom scores and 75 scores = 0) (Table 4.6, symptom flag 8). This was largely a problem with 3 subjects: 2485, 2490 and 2494, with nearly half of this flag going to 2490. This places serious doubt on the reliability of the nocturnal asthma reports of these subjects. The nocturnal asthma variable will not be analyzed in this report.

One method of detecting whether records were not filled out daily is by observing whether pen marks appear to be the same for an entire 1-week diary sheet (Table 4.6, symptom flag 7). This was repeatedly seen for three subjects: 2474, 2483 and 2487. These subjects also had a low frequency of missing data. Recall that 2487 was a subject with the highest frequency of replicate PEFs as well. Therefore, the pen marks serve to support the belief that 2487's data is in large part falsified and entered all at one time per week.

Table 4.6. Session counts for problems with health outcome data by individual subjects: Asthma Panel Study, Huntington Park region, Oct 21, 1999 to Jan 23, 2000

	Missing Sx Score, but Entered Time of Sxs (Sxflag=2)	Symptom score of 0 entered, but time of severity entered (Sxflag=3)	Missing Sx Score, but Subject Verbally Reports Having no Symptoms (Sxflag=9)	Awakened at Night by Asthma but Sx Score=0 (Sxflag=8)	Penmarks the Same all Week (Sxflag=7)	Extreme Variation in Respiratory Infections (Allergy?) (Sxflag=11)	Number Changed (Sxflag=5,10 Rxflag=4)	prn MDI Data Missing, but Subject Verbally Reports No Use (Rxflag=3)	Anti-inflam. Med. intermit-tent use (Rxflag= 1, 2)[a]	Missing Sx Data	Total Obs.
2468			20				1	46		34	74
2469	2	4		4			2	50		5	77
2470		1						6			44
2472		3					4	1			79
2473											45
2474					81		2	11		2	81
2483					20		2	72		1	75
2484		5		4			6	15			47
2485		16		11		53	2	51			55
2486	2	7		1			27	46		2	55
2487					53					5	53
2488		2	11	2			3	11		22	84
2489						46	1			1	46
2490	15	34		44					18	19	64
2491	11	3	23	1			2	82		34	83
2492			6				1			6	53
2494		33		14							49
2495		46		2				4			48
2496							1		7		81
2497		2		4			1	36			80
2498			1							1	35
2499											39
2500							1	1		1	54
2501				4							64
Total	30	156	61	91	154	99	56	432	96	133	1465

[a] includes preventive anti-inflammatory medications intended for regularly scheduled use and excludes use of oral prednisone for asthma flares.

Respiratory infection data for 2485 and 2489 appears to be in error because of the frequent off and on appearance of responses, which is inconsistent with the usual course and frequency of respiratory infections (Table 4.6, symptom flag 11). It appears in a pattern similar to the way allergy symptoms might present. Therefore, we cannot use this as a control variable for these two subjects. Recall that 2485 also had difficulty with the nocturnal asthma question.

Medication flags (Rxflag) were also used. When numbers are erased and changed, it raises the suspicion that errors may have occurred (Table 4.6, symptom flag 5, 10, medication flag 4). This occurred frequently with one subject, 2486. For numerous days (432) subjects did not enter anything under use of as-needed inhaler medications, despite reports at baseline that inhalers were available (Table 4.6, medication flag 3). RLANRC staff received weekly reports from subjects that they left it blank because of no use. In all subjects doing this, there were no positive entries, suggesting that subjects never used their inhaler. However, for one subject (2491) there were numerous positive entries for 3 inhalers, more clearly suggesting that blanks were zeros. The subject verbally confirmed this to research staff. We have flagged the data, but coded blanks zeros for this subject. The remaining subject data with no apparent inhaler use are left missing.

Two subjects used anti-inflammatory medications either on an as-needed basis or intermittently due to noncompliance with medication prescription, but recorded their use under as-needed inhaler responses (Table 4.6, medication flags 1, 2). Generally, anti-inflammatory medications are intended for preventive maintenance. We coded these anti-inflammatory medications by name as with other regularly prescribed medications, and did not code them as-needed along with beta-agonist medications.

Out of all diary days for the 24 subjects, missing symptom scores were found on 133 days or 9.1% of total possible entries (1465), and only one entry for symptoms was unreadable yielding a total of 1,332 person-days of symptom diary observations. Therefore, we were just 12 observations short of the proposed project goal of obtaining 1,344 person-days. Dropping two subjects with highly suspect data (IDs 2484, 2487) there were 1,243 person-days of symptom diary observations in the remaining 22 subjects. Additionally dropping two subjects with invalid respiratory infection data for 2485 and 2489 there were 1,144 person-days of asthma symptom diary observations in the remaining 20 subjects for all days including run-in days and days with no ambient pollution data. There were 1,035 symptom-days of observation in these 20 subjects over the period with outdoor pollution data (Nov. 4, 1999 through Jan. 23, 2000). In the regression analysis sections, the number of person-days with available data for multivariate regression models is discussed.

***4.2.5. Assessment of Epidemiologic Data Quality for the Analysis of Breath VOCs*:** The following focuses on the quality of daily data from the subset of days when subjects gave VOC breath samples. After receiving VOC breath data from RTI, we conducted an evaluation of reports by subjects of their asthma status during the day they performed the breath-sampling maneuver. Subjects verbally reported to a research assistant who picked up the used canister whether they had an asthma event when giving the sample or no event (baseline). Recall that the baseline attribute was instructed to subjects to mean no asthma symptoms that day or the previous two days. RLANRC staff coded the subject's status when collecting breath canisters. They instructed subjects to perform maneuvers on both event and baseline days without collecting too many of one or the other type of sample. Below, we present a comparison of this event versus baseline data with contemporaneous diary reports from the subjects for asthma symptom severity and as-needed medication use.

Of 141 valid canisters collected, 73 (52%) were recorded as being at baseline and 68 (48%) were recorded as asthma events. Except for 9 canisters in which the baseline and event samples were 1-2 days apart, a

minimum of 3 days were found between the event and baseline. However, only four of these 9 canisters showed diary symptom scores that were zero for one of the paired days and over 0 for the other day.

The availability of diary data to match days when canisters were collected was less than expected. A total of 18 canister days had no diary data. Nine of these observations occurred because subjects had completed diary follow-up before the Christmas holiday period, but continued to give breath samples. Two other observations are from ID 2471 and one is from ID 2493, both of who were dropped from the study because of noncompliance, and their diary data was not coded due to this. The remaining 7 missing diary observations represent gaps in the subjects' follow-up due to noncompliance. An additional 9 observations had missing asthma symptom score data but other health outcomes, primarily PEF, were reported.

To compare event versus baseline data with contemporaneous diary reports of asthma symptoms, the ordinal symptom score (0 to 5) was dichotomized in three ways. As described above in Section 2.13.1., this was intended to capture different severities of asthma according to the impact of symptoms on subjective perceptions of asthma and on daily activities. The first cut-point was between no symptoms (score 0) versus any; the next cut-point was between no symptoms or symptoms not bothersome (score 0 or 1) versus bothersome or worse symptoms (score > 1); the final cut-point was none to bothersome symptoms, but no interference with daily activities (score 0-2), versus asthma symptoms that interfered with daily activities (score > 2). As-needed β-agonist inhaler is also an indication of asthma activity. Recall that subjects were instructed that if they required the use of such inhalers for asthma exacerbations that this would be considered an asthma event. Thus, there were 5 basic types of asthma outcomes that could reflect asthma severity: event/baseline classification, as-needed inhaler use, and ordinal asthma symptom scores (dichotomized 3 ways). It is of interest to test whether the each of the 4 asthma outcome measures recorded in the diaries were correlated with the binary classification of the VOC canisters. Alternate measures reliability was tested with the Kappa coefficient (κ) defined as follows:

$$\frac{\text{Observed agreement} - \text{Expected agreement}}{1 - \text{Expected agreement}}$$

Where expected agreement is that which occurs by chance if the two measures are completely unrelated, or:

$$p_1 p_2 + (1 - p_1)(1 - p_2)$$

where, p_1 is the proportion classified as having the outcome by the first imperfect classification and p_2 is the proportion classified as having the outcome by the second imperfect classification.

Therefore, κ has the characteristic of correcting for chance agreement. When two measurements agree only due to chance, κ is zero, whereas for perfect agreement, κ is one. In general, it is agreed that κ coefficients less than 0.40 are considered to show poor agreement; 0.40-0.64 are modest agreement; 0.65-0.74 are good; and > 0.75 are excellent.

Table 4.7 shows results of comparisons between diary outcomes and classifications of event versus baseline recorded for the VOC canisters. As discussed in Section 4.2.4., there were numerous missing observations for as-needed inhaler use. This occurred primarily due to subject noncompliance in filling in a zero for no inhaler use, which in many cases covered most or all days for many subjects because of the mild intermittent nature of their asthma. Reliability of inhaler use with asthma event versus baseline coding was poor. It is possible that for some of the 13 disagreements of no inhaler use despite asthma events, the subjects may have needed an inhaler due to symptoms but were noncompliant with the appropriate use of as-needed asthma medication. There is no clear explanation for why there was as-needed inhaler use on 15 baseline days. The correspondence was also poor between event-baseline

canister classification and dichotomizations of the ordinal asthma symptom scores. In fact for 24 so-called event canisters, the asthma symptom severity was coded as zero, i.e., no symptoms.

Table 4.7. Distribution of reports of asthma status on breath maneuver days as compared with asthma outcomes reported in subject diaries: Asthma Panel Study, Huntington Park region, Nov. 1, 1999 to Jan. 23, 2000

	Asthma Status on Breath Maneuver Day:[a]		
Diary Variable	Baseline (row %)	Asthma Event (row %)	Kappa Coefficient (95% CI)
As-needed Metered Dose Inhaler Use:			
None	25 (66)	13 (34)	
Any	15 (39)	23 (61)	0.26 (0.05, 0.48)
Missing Diary Observations	33	32	
Asthma Symptoms:[b]			
None	48 (67)	24 (33)	
Any	10 (24)	31 (76)	0.39 (0.23, 0.56)
Missing Diary Observations	15	13	
Asthma Symptoms:			
None or not bothersome	52 (58)	38 (42)	
Bothersome or Worse	6 (26)	17 (74)	0.21 (0.06, 0.36)
Missing Diary Observations	15	13	
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	55 (52)	51 (48)	
Interfering with Daily Activities or Worse	3 (43)	4 (57)	0.02 (-0.07, 0.11)
Missing Diary Observations	15	13	

[a] Subject report of whether they had an Asthma Event, defined for subjects as meaning that asthma symptoms occurred that required the use of as-needed ß-agonist medications, whereas Baseline means no symptoms that day and the previous two days.

[b] Asthma symptom severity was an ordinal score from 0 to 5 and dichotomized using 3 different cut-points as described for the 3 comparisons.

4.2.6. Conclusions Regarding Epidemiologic Data Quality: We conclude that PEF data for two subjects are highly suspect and may include a large proportion of faked data (IDs 2484, 2487), and several others had difficulty with PEF maneuvers. We suspect that other data, including symptom data, are invalid for these two subjects. Therefore, some subject data were subjected to tests excluding potentially invalid observations in a sensitivity analysis of exposure-response relationships. First, all PEF data for 2484 and 2487 were excluded from regression models. Second, symptom data for 2484 and 2487 were included then excluded from regression models to examine the influence on regression parameters and standard

errors. Also, respiratory infection data for 2485 and 2489 were excluded from analysis. Finally, PEF data showing within-maneuver reproducibility > 10% were excluded from regression models.

We also conclude that the classification of canister data as event versus baseline may be in error. Given the poor agreement of diary data with the canister classification, a preliminary analysis of the relationships of VOCs to asthma symptom severity will examine both diary symptom data and the canister classification. Below diary symptom score variables are compared with the event/baseline classification in regressions on breath VOCs. The canister classification has the advantage of 28 more observations than the symptom diary data. Regardless, if there is a true underlying relationship, and one asthma symptom outcome measure is more accurate than the other, it is possible that associations could be found for the more accurate outcome but not the inaccurate outcome. Inhaler use will not be examined because of the low frequency of non-missing data.

4.3. Analysis of Effects of Exhaled Breath VOCs

***4.3.1. Subject Data for the Analysis of Exhaled Breath VOCs*:** Table 4.8 shows overall characteristics of subjects for panel days when they gave VOC breath samples. One subject did not give any useable breath samples. The table excludes the two noncompliant subjects described above, which leaves 21 subjects with breath VOC data for the final regression analyses. We present results of regression models below including the two subjects for comparison.

Table 4.8. Descriptive statistics for 21 asthmatic children who gave VOC exhaled breath samples Nov 1, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Subject Characteristic	
Median age (age Range)	12 (10-16)
No. males / females	17 / 4
No. days asthma symptoms interfered with daily activities / person-days (%)[a]	5 / 108 (4.6%)
No. days asthma symptoms were bothersome or worse / person-days (%)[a]	21 / 108 (19.4%)
No. subjects with mild persistent or more severe asthma[b]	5 (24%)
No. subjects with percent predicted FEV_1 < 80% at panel beginning and end	5 (24%)
No. subjects taking regularly scheduled anti-inflammatory medications	6 (30%)
Mean daily as-needed β-agonist inhaler puffs (SD)	1.90 (1.88)

[a] From subset of person-days when subject gave VOC breath samples.
[b] Defined as daily diary reports of symptoms on > 2 times a week throughout the study (NHLBI, 1997), irrespective of asthma medication regimen, from all person-days of observation during then study.

***4.3.2. Exposure Data for the Analysis of Health Effects of Exhaled Breath versus Ambient VOCs*:**
Table 4.9 shows univariate statistics for exposure data available from the subset of days when 21 subjects gave exhaled breath samples for VOCs. Ambient VOC data in Table 4.9 are from the stationary outdoor monitoring sites. They are limited to those compounds measured in breath, and match the available person-days of observation for breath VOCs. This is because we will compare exposure-response relationships between breath and ambient measurements. There were fewer person-days of observation for ambient than for breath VOC measurements because of sampling or deployment problems. Differences in the number of observations between the specific breath VOCs was due to inability to calculate the concentration from GC-MS interference, particularly for Methylene Chloride. There was no ambient VOC monitoring Dec 25 through 26, and Dec 31 through Jan 4. Many days for ambient styrene (41) and ambient *p*-dichlorobenzene (24) were below the method detection limit (MDL); for these days, values were set at half the MDL (0.05 ppb).

Table 4.9. Exhaled breath and outdoor ambient measurements of volatile organic compounds, Nov 1, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California

Exposure & Averaging Time	No. Obs.[a]	Mean (SD)	Median	Minimum / Maximum	90th Percentile
Breath VOCs (ng/L)					
Benzene	102	2.19 (2.72)	1.56	0.20 / 24.46	3.51
Methylene Chloride	78	2.73 (4.33)	1.75	0.49 / 25.40	3.83
Styrene	99	1.51 (0.99)	1.37	0.18 / 5.92	2.90
Toluene	101	8.28 (10.40)	5.70	2.00 / 69.68	15.19
m,p-Xylene	106	4.21 (5.98)	2.65	0.09 / 47.18	5.72
o-Xylene	105	1.47 (1.72)	1.03	0.11 / 11.51	2.03
p-Dichlorobenzene	98	36.29 (94.87)	1.56	0.16 / 490.76	225.31
Tetrachloroethylene	105	4.40 (10.77)	1.99	0.24 / 77.89	5.59
Ambient VOCs (ng/L)[b]					
Benzene	88	5.67 (2.68)	5.42	0.96 / 13.7	9.24
Methylene Chloride	88	4.30 (3.26)	3.12	1.04 / 16.29	8.66
Styrene [c]	88	0.51 (0.34)	0.43	0.21 / 1.70	0.85
Toluene	88	26.9 (13.5)	26.3	7.1 / 72.9	43.2
m,p-Xylene	88	13.3 (7.33)	13.0	1.30 / 39.4	20.8
o-Xylene	88	4.16 (2.43)	3.68	0.43 / 13.0	6.94
p-Dichlorobenzene [c]	88	0.96 (0.54)	1.20	0.30 / 2.40	1.80
Tetrachloroethylene	88	3.52 (2.17)	3.05	0.34 / 9.47	6.09

[a] The number of ambient observations used in univariate statistics is the person-days of exposure data available from the subset of days when 21 subjects gave exhaled breath samples for VOCs. Fewer person-days of observation were obtained for ambient than for breath measurements due to sampling or deployment problems. Differences in the number of breath VOCs is due to inability to calculate concentration from GC-MS interference, particularly for Methylene Chloride.

[b] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites. There was no ambient VOC monitoring Dec 25 through 26, and Dec 31 through Jan 4.

[c] Many days for ambient styrene (41) and ambient p-dichlorobenzene (24) were below the method detection limit (MDL); for days below the MDL, values were set at half the MDL (0.05 ppb).

Table 4.10 shows outdoor ambient measurements of criteria air pollutant gases from the subset of days when subjects gave exhaled breath samples for VOCs. Concentrations were low, with all maximum values being below the U.S. NAAQS.

Table 4.10. Outdoor ambient measurements of criteria air pollutant gases, from the subset of days when subjects gave exhaled breath samples for VOCs from Nov 11, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.[a]

Exposure & Averaging Time	No. Obs.[b]	Mean (SD)	Median	Minimum / Maximum	90th Percentile
O_3 1-hr max (ppb)	82	25 (11)	22	8 / 52	42
O_3 8-hr max (ppb)	82	17 (8)	15	5 / 37	29
NO_2 1-hr max (ppb)	77	7 (2)	7	3 / 13	9
NO_2 8-hr max (ppb)	77	6 (2)	6	3 / 11	8
SO_2 1-hr max (ppb)	82	7 (5)	7	2 / 26	10
SO_2 8-hr max (ppb)	82	5 (4)	5	1 / 20	7
CO 1-hr max (ppb)	82	7 (3)	8	2 / 17	11
CO 8-hr max (ppb)	82	5 (2)	5	2 / 10	8
Temperature 1-hr max (°F)	106	72 (7)	71	50 / 87	80

[a] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites.

[b] To maintain comparability to breath VOC data in Table 4.8, the number of ambient observations used in univariate statistics is the person-days of exposure data available from the subset of days when 21 subjects gave exhaled breath samples for VOCs.

Table 4.11 shows the correlation matrix between breath and ambient VOCs. Correlations were low between like VOCs (diagonal row in dark font) and significant only for benzene and tetrachloroethylene. Both ambient and breath benzene were correlated with several of the other VOCs in breath or in ambient air, respectively. Breath benzene and tetrachloroethylene were weakly, but significantly, correlated with most of the ambient VOCs. This table examines the correlation between current day breath VOCs with current day ambient VOCs. However, it is known that for this group of VOCs, residence time ranged from 44 hrs (trichloroethylene) to 84 hr (toluene) for the fourth phase (Wallace et al., 1996). Thus, a large peak in toluene exposure that occurred in ambient can still be measured in breath even if the ambient source is gone. It is possible that many these peak exposures during our study period led to breath and ambient measurements being "out of sync" because we never knew when the peak occurred. From a pharmacokinetic perspective, however, the longer the residence time, the better the correlation, even with other VOCs, because the VOCs with longer residence time will be in exhaled breath longer whereas the ones with shorter residence time "come and go". Unfortunately, the work by Wallace et al., did not provide the residence times for benzene, tetrachloroethylene and methylene chloride. However the available data have the following sequence in terms of residence time: Toluene (84 hrs) > o-xylene (64 hrs). Notice the magnitude of correlation in the last row of Table 4.11 follows this order.

Table 4.11. Same day breath and ambient VOC correlation matrix,[a] Nov 1, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

	Ambient							
Breath	Benzene	Methylene Chloride	Styrene	Toluene	m,p-Xylene	o-Xylene	p-Dichlorobenzene	Tetrachloroethylene
Benzene	**0.30****	0.30**	-0.01	0.36†	0.33**	0.28*	0.15	0.28*
Methylene Chloride	0.13	**0.21**	-0.26	0.12	0.1	0.05	-0.04	0.14
Styrene	0.07	0.01	**0.20**	0.05	0.11	0.11	0.21	0.06
Toluene	0.19	0.12	-0.01	**0.22**	0.16	0.15	0.11	0.14
M,p-Xylene	0.24*	0.09	0.05	0.16	**0.18**	0.18	0.1	0.13
o- Xylene	0.25*	0.09	0.09	0.16	0.18	**0.18**	0.09	0.13
p-Dichlorobenzene	-0.13	-0.14	-0.18	-0.05	-0.13	-0.17	**-0.14**	-0.15
Tetrachloroethylene	0.19	0.38†	0.25*	0.40†	0.33**	0.33**	0.29**	**0.31****

[a] Spearman correlation coefficients; The number of paired breath versus ambient observations is 82 for Benzene, 58 for Methylene Chloride, 79 for Styrene, 83 for Toluene, 86 for M,p-Xylene, 86 for o-Xylene, 79 for p-Dichlorobenzene, and 85 for Tetrachloroethylene.

* $p < 0.05$; ** $p < 0.01$; † $p < 0.001$;

4.3.3. Preliminary Regression Analysis of Asthma Symptoms and Exhaled Breath VOC Data: Determining Binary Cut-off Points, Control Variables, and the Influence of Potentially Unreliable Diary Data

The baseline/event data and three binary symptom score variables (as described above) were analyzed as dependent variables with generalized estimating equations (GEE) using the logit link in the SAS procedure Genmod (see Methods). The best working correlation was found to be exchangeable correlation. Odds ratios and 95% confidence intervals (CI) for symptom models are expressed at mean VOC levels (mean effects).

Only VOC data flagged as acceptable by RTI were included in the analysis. Four compounds were not included because breath VOC data were below the method-detection limit for more than 80% of the samples: 1,1-dichloroethane, carbon tetrachloride, chloroform, and o-dichlorobenzene. Carbon tetrachloride and chloroform had only 9 and 17 person-observations above the limit of detection, respectively.

Regression models were tested excluding, then including, the two subjects with unreliable PEF and other diary data (2484 and 2487) as described above. These subjects contributed 6 baseline and 4 event canisters. Then, models also excluding the two subjects with invalid respiratory infection data (2485 and 2489) were tested and compared with models including these subjects.

Table 4.12 shows results of GEE models for the asthma outcomes versus breath VOCs with no covariates in the model. Most models gave no suggestion of an adverse effect (p-values > 0.2), including those for methylene chloride, styrene, tetrachloroethylene, *m,p*-xylene, *o*-xylene, and *p*-dichlorobenzene. The benzene models were suggestive of a positive association, but not significant. There was a significant positive association of asthma symptoms causing interference with daily activities (symptom scores > 2) with toluene.

The models for benzene and toluene alone were also tested including the two subjects with unreliable diary data (2484, 2487) previously described. Compared with models excluding these subjects (Table 4.12), models including the two subjects consistently led to diminished ORs and usually increased standard errors for all models, suggesting that their data biased estimates toward the null hypothesis. An example of this is shown below for benzene and toluene. Models including these two subjects as compared to models excluding them (Table 4.12) showed, respectively, the following:

- OR for an asthma symptom score >1 versus benzene: decreased to 1.92 ($p < 0.12$) from 2.06 ($p < 0.10$);
- OR for an asthma symptom score >2 versus benzene: decreased to 1.52 ($p < 0.26$) from 1.87 ($p < 0.13$);
- OR for an asthma symptom score >1 versus toluene: decreased to 1.73 from 1.84, both $p < 0.35$;
- OR for an asthma symptom score >2 versus toluene: decreased to 1.91 ($p<0.03$) from 2.38 ($p < 0.007$).

The benzene and toluene models were further tested for confounding by: 1) temperature measured at the central sites (Heliotrope School to Nov. 8, then Nimitz School); 2) respiratory tract infections; and 3) weekend. Two-pollutant models with one VOC and one central site criteria air pollutants are considered separately in this report. Control variables were selected for multivariate models if p-values were < 0.15 for a model including only the control variable. This is justifiable given the small cell sizes for binary symptom categories, particularly for the risk of more severe asthma symptom scores, and given a low expectation of group confounding by several control variables rather than individual control variables.

We first examined GEE models for the relationship of respiratory infections and of weekend to breath VOC concentrations. There were small nonsignificant relationships of respiratory infections to breath benzene (OR 2.26, 95% CI 0.62, 8.25) and to breath toluene (OR 1.41, 95% CI 0.18, 10.7). Breath VOCs were not significantly different across weekend versus weekdays (e.g., benzene, p=0.83; toluene, p=0.11).

Spearman correlations between breath VOCs and temperature were very small ($r < 0.13$) and nonsignificant (e.g., benzene, $p = 0.32$; toluene, $p = 0.75$).

We then examined the relationship of the asthma outcomes to respiratory infections, weekend and temperature. Each independent control variable was tested alone in GEE models. As discussed above, respiratory infection data for 2485 and 2489 was in error and was excluded.

There was a borderline significant positive association between asthma events and reports of respiratory infections (OR for an asthma event given a respiratory infection, 2.72, 95% CI 0.82, 8.97, $p < 0.11$). Respiratory infection reports were significantly associated with asthma symptom scores > 0 (OR 4.86, 95% CI 1.59, 14.8, $p < 0.01$), scores > 1 (OR 4.82, 95% CI 2.42, 9.60, $p < 0.0001$), and scores > 2 (OR 7.27, 95% CI 2.86, 18.5, $p < 0.0001$). Therefore, diary reports of asthma symptoms were notably closer to expectations of a positive relationship between asthma and respiratory infections than the asthma event coding of canisters.

Asthma event compared with baseline canisters were significantly more likely on weekends than weekdays (OR 2.50, 95% CI 1.26, 4.95, $p < 0.01$). However, there was no such association for reports of asthma symptom scores > 0 (OR 0.84, 95% CI 0.58, 1.21, $p = 0.34$), scores > 1 (OR 0.92, 95% CI 0.54, 1.58, $p = 0.77$), or scores > 2 (OR 0.92, 95% CI 0.56, 1.52, $p = 0.76$).

Maximum daily temperature was not associated with asthma baseline versus event coding for breath VOC canisters ($p = 0.41$), but was positively associated with asthma symptom scores > 0 (ß = 0.0246, $p < 0.05$). Borderline significant associations with temperature were shown for risk of asthma symptom scores > 1 (ß=0.0401, $p < 0.07$), but scores > 2 were not associated with temperature (ß = 0.0329, $p = 0.34$).

Given the above findings, multivariate GEE models were tested for the risk of asthma outcomes from breath levels of benzene and toluene (VOCs where univariate GEE models suggested a possible relationship to asthma symptoms). These models were as follows:

1) models for the risk of asthma events were tested controlling for respiratory infections and weekend;
2) models for the risk of asthma symptom scores > 0 and > 1 were tested controlling for temperature and respiratory infections; and
3) the models for the risk of asthma symptom scores > 2 were tested controlling for respiratory infections.

Table 4.12. The relationship between asthma symptoms and breath concentrations of volatile organic compounds measured on the same day, univariate pollutant regression models, Huntington Park region Asthma Panel Study.

Benzene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	65	1.67 (0.56)	referent
Asthma Event	60	1.85 (0.65)	1.34 (0.82, 2.18)
Asthma Symptoms:[d]			
None	68	1.71 (0.66)	referent
Any	34	1.81 (0.52)	1.19 (0.47, 3.04)
Asthma Symptoms:			
None or not bothersome	83	1.66 (0.61)	referent
Bothersome or Worse	19	2.16 (0.56)	2.06 (0.85, 4.96)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	97	1.73 (0.62)	referent
Interfering with Daily Activities or Worse	5	2.11 (0.22)	1.87 (0.83, 4.21)

Methylene Chloride

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	47	1.98 (0.95)	referent
Asthma Event	49	1.98 (0.52)	0.99 (0.45, 2.17)
Asthma Symptoms:[d]			
None	52	1.94 (0.90)	referent
Any	26	1.96 (0.42)	0.99 (0.51, 1.95)
Asthma Symptoms:			
None or not bothersome	63	1.93 (0.82)	referent
Bothersome or Worse	15	2.01 (0.46)	1.10 (0.50, 2.44)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	74	1.94 (0.77)	referent
Interfering with Daily Activities or Worse	4	2.05 (0.49)	1.00 (0.49, 2.06)

Table 4.12 (continued)

Styrene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	60	1.38 (0.43)	referent
Asthma Event	58	1.36 (0.46)	0.98 (0.50, 1.91)
Asthma Symptoms:[d]			
None	64	1.41 (0.42)	referent
Any	35	1.26 (0.42)	0.62 (0.21, 1.83)
Asthma Symptoms:			
None or not bothersome	81	1.38 (0.40)	referent
Bothersome or Worse	18	1.26 (0.53)	0.66 (0.13, 3.22)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	96	1.36 (0.42)	referent
Interfering with Daily Activities or Worse	3	1.27 (0.52)	2.06 (0.13, 33.3)

Toluene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	63	5.95 (0.88)	referent
Asthma Event	61	6.32 (1.28)	1.20 (0.64, 2.24)
Asthma Symptoms:[d]			
None	67	5.67 (1.06)	referent
Any	34	6.06 (1.03)	1.26 (0.48, 3.33)
Asthma Symptoms:			
None or not bothersome	84	5.61 (1.02)	referent
Bothersome or Worse	17	6.85 (1.17)	1.84 (0.52, 6.51)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	98	5.76 (1.06)	referent
Interfering with Daily Activities or Worse	3	7.45 (0.40)	2.38 (1.27, 4.47)**

Table 4.12 (continued)

Tetrachloroethylene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	64	2.95 (1.03)	referent
Asthma Event	64	2.24 (0.78)	0.52 (0.24, 1.09)
Asthma Symptoms:[d]			
None	67	2.67 (1.18)	referent
Any	38	2.31 (0.50)	0.72 (0.46, 1.11)
Asthma Symptoms:			
None or not bothersome	84	2.50 (1.04)	referent
Bothersome or Worse	21	2.69 (0.60)	1.13 (0.64, 2.01)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	100	2.51 (0.98)	referent
Interfering with Daily Activities or Worse	5	3.15 (0.31)	1.45 (0.75, 2.81)

m,p-Xylene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	66	3.42 (0.76)	referent
Asthma Event	63	2.98 (0.87)	0.65 (0.28, 1.53)
Asthma Symptoms:[d]			
None	69	3.24 (0.82)	referent
Any	37	2.87 (0.73)	0.75 (0.26, 2.14)
Asthma Symptoms:			
None or not bothersome	86	3.09 (0.74)	referent
Bothersome or Worse	20	3.15 (1.00)	1.09 (0.32, 3.70)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	101	3.11 (0.81)	referent
Interfering with Daily Activities or Worse	5	3.03 (0.26)	1.16 (0.53, 2.51)

Table 4.12 (continued)

o-Xylene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	64	1.30 (0.48)	referent
Asthma Event	63	1.18 (0.54)	0.77 (0.39, 1.52)
Asthma Symptoms:[d]			
None	69	1.26 (0.50)	referent
Any	36	1.11 (0.50)	0.69 (0.27, 1.76)
Asthma Symptoms:			
None or not bothersome	85	1.20 (0.46)	referent
Bothersome or Worse	20	1.27 (0.66)	1.20 (0.46, 3.18)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	101	1.21 (0.51)	referent
Interfering with Daily Activities or Worse	4	1.18 (0.20)	0.99 (0.53, 1.83)

p-Dichlorobenzene

Dependent Variable	No. Obs.	Geometric Mean (Geometric SD) (ng/L)	OR (95% CI) [a] per Arithmetic Mean Concentration Increase[b]
Asthma Status on Breath Maneuver Day:[c]			
Baseline	60	4.22 (4.25)	referent
Asthma Event	58	4.51 (3.82)	1.04 (0.90, 1.21)
Asthma Symptoms:[d]			
None	63	4.21 (4.23)	referent
Any	35	3.73 (3.41)	0.96 (0.56, 1.65)
Asthma Symptoms:			
None or not bothersome	80	3.60 (3.85)	referent
Bothersome or Worse	18	6.49 (4.03)	1.33 (0.86, 2.06)
Asthma Symptoms:			
None to Bothersome but no Interference with Daily Activities	95	4.10 (4.01)	referent
Interfering with Daily Activities or Worse	3	2.36 (0.53)	0.86 (0.62, 1.20)

Table 4.12 (continued)

* p<0.05; ** p<0.01;

[a] Odds Ratios (OR) and 95% confidence intervals (CI) are from generalized estimating equations, and estimates the relative risk of a symptom response among 21 asthmatic children for a arithmetic mean change in log transformed VOC breath concentration.

[b] Mean VOC concentration is for days with non-missing diary data and is shown in Table 4.9

[c] Subject report of whether they had an Asthma Event, defined as symptoms that required the use of as-needed ß-agonist medications, where Baseline means no symptoms that day and the previous two days.

[d] Asthma symptom severity was an ordinal score from 0 to 5 and dichotomized using 3 different cut-points for the 3 models as described.

Table 4.13 shows the results of these models and allows a comparison of models of breath VOC alone to models of VOC with the control variables. The single pollutant models are compared with the multivariate models controlling for respiratory infections after excluding observations for the 2 subjects with invalidated respiratory infection data. Recall that subject 2485 had a high frequency of other errors coding asthma symptoms. Data for two subjects with unreliable diary data (2484, 2487) were also excluded as in Table 4.12 models.

Multivariate models in Table 4.13 for the risk of asthma events (canister classification) from breath VOCs were all non-significant and showed all ORs were generally not far from 1.0. Models for the risk of asthma symptom scores > 0 or > 1 from benzene were not confounded by respiratory infections or temperature. The model for the risk of asthma symptom scores > 2 from benzene was also not confounded by respiratory infections, and the association was slightly larger than the model with benzene alone. Both single pollutant and multivariate models for scores > 2 versus benzene were statistically significant ($p < 0.01$). This is in contrast to the model in Table 4.12 that includes the two subjects with invalid respiratory infection data, suggesting that their symptom data biased estimates toward the null hypothesis. The respiratory infection variable was still significant in the multivariate models with benzene (data not shown).

Model fit for the risk of asthma symptom scores > 0 or > 1 from toluene was marginally improved with the covariates respiratory infections or temperature, and toluene parameters remained non-significant. Models for the risk of asthma symptom scores > 1 from breath toluene suggested possible confounding by respiratory infections and temperature, but confidence intervals were wide. The decrease in the parameter estimate for toluene was attributable to temperature. The multivariate model for the risk of asthma symptom scores > 2 from toluene did not converge due to additional missing respiratory infection observations in the model.

Table 4.13. The relationship between asthma symptoms and breath concentrations of volatile organic compounds, multivariate regression models, Asthma Panel Study, Huntington Park region.

Dependent Variable	**Benzene** OR (95% CI)[a] per Arithmetic Mean Concentration Increase		**Toluene** OR (95% CI) per Arithmetic Mean Concentration Increase	
	VOC alone model	Multivariate model	VOC alone model	Multivariate model
Asthma Status on Breath Maneuver Day:[b]				
Baseline	referent	referent	referent	referent
Asthma Event	1.23 (0.76, 1.98)	1.02 (0.65, 1.60)	1.09 (0.56, 2.11)	0.63 (0.27, 1.50)
Asthma Symptoms:[c]				
None	referent	referent	referent	referent
Any	1.28 (0.49, 3.36)	1.42 (0.55, 3.64)	1.16 (0.41, 3.26)	1.37 (0.48, 3.94)
Asthma Symptoms:				
None or not bothersome	referent	referent	referent	referent
Bothersome or Worse	2.17 (0.84, 5.56)	2.03 (0.80, 5.11)	1.80 (0.50, 6.48)	1.58 (0.43, 5.79)
Asthma Symptoms:				
None to Bothersome but no Interference with Daily Activities	referent	referent	referent	referent
Interfering with Daily Activities or Worse	2.48 (1.30, 4.75)**	2.56 (1.26, 5.21)**	2.34 (1.24, 4.41)**	NC

* $p<0.05$; ** $p<0.01$; † $p<0.001$; NC = non-convergence of GEE model due to an insufficient number of symptom events.

[a] Odds Ratios (OR) and 95% confidence intervals (CI) are from generalized estimating equations, and estimates the relative risk of a symptom response among 19 asthmatic children for a arithmetic mean change in log transformed VOC breath concentration. Two subjects with invalid respiratory infection data are excluded from both VOC alone and multivariate models.

[b] Subject report of whether they had an Asthma Event, defined as symptoms that required the use of as-needed ß-agonist medications, where Baseline means no symptoms that day and the previous two days. These models control for respiratory infections and weekend.

[c] Asthma symptom severity was an ordinal score from 0 to 5 and dichotomized using 3 different cut-points for the 3 models as described. Models for the first two dependent variables for Asthma Symptoms control for temperature and respiratory infections; models for the third dependent variable control for respiratory infections

Results excluding 4 subjects with potentially unreliable data out of 24 total subjects suggest that models are somewhat sensitive to errors in subject health outcome data. In general, we found that after the suspect data were removed, the magnitudes of association increased and standard errors decreased. The following analyses exclude diary data for these subjects. Furthermore, results were more robust for bothersome or more severe symptom data reported in diaries as compared with the event/baseline classification of the canisters. Also, including symptoms that were not bothersome as a positive outcome led to smaller regression parameters. Therefore, the following regression analyses will focus on diary symptoms scores dichotomized into:

1) no symptoms or symptoms not bothersome (score 0 or 1) versus bothersome or more severe asthma symptoms (***symptom scores > 1***); and
2) none to bothersome symptoms, but no interference with daily activities (score 0-2), versus asthma symptoms that interfered with daily activities (***symptom scores > 2***).

Also, only 8 out of 110 reports (7%) stated that asthma symptoms were bothersome or worse on the day with breath benzene data lagged 1 day, in contrast to 18 out of 95 (19%) of such symptom reports on the same day with breath benzene data (lag day 0). It is for this reason that analyses of lagged breath VOCs were not performed for symptoms.

4.3.4. Regression Analysis of Asthma Symptoms and VOCs in Exhaled Breath versus Ambient Air:

Before comparing ambient to breath VOC relationships to asthma symptoms, we first tested for covariate confounding in ambient VOC models. We found a small amount of confounding of ambient benzene by temperature. Odds ratios were as follows: for the model with ambient benzene alone, the OR was 6.54 (95% CI, 2.02, 21.1); and for the multivariate model with temperature, the OR was 6.06 (95% CI, 1.69, 21.7). For ambient toluene, we found a small amount of positive confounding by respiratory infections and negative confounding by temperature. Odds ratios were as follows: for the model with ambient toluene alone, the OR was 5.19 (95% CI, 1.43, 18.8); for the multivariate model with respiratory infections, the OR was 5.66 (95% CI, 1.58, 20.3); and for the multivariate model with temperature, the OR was 4.96 (95% CI, 1.38, 17.8). A pattern of modest confounding similar to that of ambient toluene and benzene was found for most of the remaining ambient VOCs as well as ambient criteria pollutant gases. Therefore, all models for both breath VOCs and ambient pollutants will control for respiratory infections and temperature. This approach will maintain comparability between the different pollutant models.

Table 4.14 shows results of the multivariate GEE models for the two binary symptom score variables (as described above) in relation to concentrations of breath VOCs as compared with ambient VOCs. Ambient VOCs are from the subset of person-days when subjects gave breath samples. Ambient benzene was significantly and strongly associated with symptom scores > 1. The pollutant mean effect on risk of symptoms was nearly six times higher than breath benzene for an increase to the mean ambient benzene level of 1.78 ppb. The odds ratio for breath benzene was also not significant ($p < 0.14$). For benzene models testing the risk of more severe symptoms interfering with daily activities (symptom scores > 2), both breath and ambient benzene were significant and similar in magnitude (OR 2.56 vs. 2.75, respectively). Ambient toluene was also significantly and strongly associated with symptom scores > 1. The pollutant mean effect on risk of symptoms was nearly five times higher than breath toluene for an increase to the mean ambient toluene level of 7.17 ppb. However, breath toluene was not associated with symptom scores > 1. Ambient toluene was also associated with symptom scores > 2, but the multivariate model for breath toluene did not converge as discussed above. Ambient *m,p*-xylene was significantly associated with both symptom variables. Breath *m,p*-xylene showed a borderline significant relationship to symptom scores > 2 ($p < 0.08$), whereas the model for the less severe symptom variable showed an OR

of 1.00. Ambient o-xylene was also associated with symptoms, but breath o-xylene was not. Neither breath nor ambient concentrations of methylene chloride, styrene, tetrachloroethylene or *p*-dichlorobenzene were significantly associated with symptoms. Compared with breath tetrachloroethylene, ambient tetrachloroethylene showed a larger OR for symptom scores > 1, consistent with relative differences for other significant ambient VOCs.

Table 4.15 shows results of GEE models for the two binary symptom score variables in relation to concentrations of ambient criteria gases measured on the same days as the breath samples. Although O_3 was not associated with symptom scores > 1, it was strongly associated with symptom scores > 2 for both 1-hr and 8-hr averaging times. One-hr and 8-hr NO_2 was strongly associated with both symptom outcome variables. The risk of asthma symptoms was seven or more times higher for an increase to the mean ambient NO_2 level. The ORs for NO_2 were notably larger for symptom scores > 2. One-hr and 8-hr SO_2 was also associated with both symptom outcome variables. The magnitudes of association for SO_2 were smaller than for NO_2, with ORs of around 2 to 3. The ORs for SO_2 were somewhat larger for symptom scores > 2. Carbon monoxide was not associated with symptoms.

The following is an analysis of confounding by criteria pollutant gases of associations between asthma symptoms and breath benzene. Breath benzene was regressed with the different criteria pollutant gases controlling for respiratory infections (Table 4.16). Parameters for both benzene and 1-hr criteria pollutant gases were reduced for the 2-pollutant model for symptom scores > 1, and the variances increased as well. Even though O_3 was not associated with symptoms using the lower cut-point (symptom score >1), the magnitude of association for benzene was reduced from an OR of 2.03 to 1.42 and the Z-score was reduced from 1.5 to 0.8. The ORs for both NO_2 and SO_2 in the 2-pollutant model decreased 39% and 16%, respectively, and were borderline significant ($p < 0.08$) whereas in the single pollutant model they were $p < 0.05$. The parameter for breath benzene was reduced by 39% and 35% in regressions with NO_2 and SO_2, respectively. For the 2-pollutant model on symptom scores > 2, both breath benzene and criteria pollutant gases remained significant or nearly so. Also, compared with the single pollutant models, effect estimates were not notably changed. Two-pollutant models using the 8-hr averaging times of the gaseous criteria pollutants (not shown) were similar to those shown in Table 4.16 for 1-hr averaging times. These results show that ambient criteria pollutant gases do not confound associations between breath benzene and more severe symptoms. However, for models predicting symptom scores > 1 there is some instability in regression parameters along with inflation of variance. The association with breath benzene was diminished with O_3 in the model even though O_3 was not associated with symptoms > 1. The NO_2 and breath benzene model shows the clearest evidence for instability with both parameters being reduced by 39%. However, the pollutants were weakly correlated with each other [Spearman's R for O_3 and benzene, –0.12 ($p < 0.3$), 1-hr NO_2 and benzene, 0.25 ($p < 0.05$), 1-hr SO_2 and benzene, 0.39 ($p < 0.001$)]. Testing for interaction between breath benzene and criteria pollutant gases showed only one significant interaction between benzene and 8-hr SO_2 (β 0.32, SE 0.16) in relation to symptom scores > 1. The parameter for an interaction term for benzene and 1-hr SO_2 was borderline significant ($p <0.08$).

Table 4.14. Relationship of asthma symptoms in children to concentrations of volatile organic compounds measured in exhaled breath samples versus ambient outdoor central sites; Nov 1, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Independent variable[a]	No. Obs.	Mean concentration (ng/L)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[c]	Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[d]
Breath Benzene	93	2.19	2.03 (0.80, 5.11)	2.56 (1.26, 5.21)**
Ambient Benzene	80	5.67	5.93 (1.64, 21.4)**	2.75 (1.61, 4.71)†
Breath Methylene Chloride	67	2.73	1.04 (0.42, 2.55)	NC
Ambient Methylene Chloride	80	4.30	1.03 (0.47, 2.29)	0.99 (0.7, 1.30)
Breath Styrene	90	1.51	0.48 (0.09, 2.44)	1.48 (0.03, 74.76)
Ambient Styrene	80	0.51	0.88 (0.35, 2.23)	1.86 (0.87, 3.96)
Breath Toluene	89	8.28	1.58 (0.43, 5.79)	NC
Ambient Toluene	80	26.9	4.96 (1.38, 17.8)*	3.06 (1.64, 5.71)†
Breath Tetrachloroethylene	95	4.40	1.07 (0.51, 2.25)	1.62 (0.84, 3.10)
Ambient Tetrachloroethylene	80	3.52	1.94 (0.80, 4.70)	1.83 (0.73, 4.58)
Breath m,p-Xylene	96	4.21	1.00 (0.28, 3.57)	1.56 (0.95, 2.56)
Ambient m,p-Xylene	80	13.3	3.61 (1.13, 11.6)*	2.83 (1.43, 5.58)**
Breath o-Xylene	95	1.47	1.20 (0.44, 3.25)	1.30 (0.79, 2.14)
Ambient o-Xylene	80	4.16	2.29 (0.89, 5.89)	2.17 (1.02, 4.63)*
Breath p-Dichlorobenzene	89	36.3	1.29 (0.82, 2.03)	0.59 (0.32, 1.06)
Ambient p-Dichlorobenzene	80	0.96	1.24 (0.39, 3.97)	1.16 (0.74, 1.81)

[a] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites. Mean values of pollutants are from the same day as symptom reports (lag 0) and from the subset of person-days (No. Obs.) when subjects gave exhaled breath samples for VOCs.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant, controlling for respiratory infections in 19 children (2 subjects with invalid respiratory infection data are excluded). Models for bothersome or more severe asthma symptoms control for temperature as well. Breath VOCs were log-transformed in models.

[c] The asthma symptom severity score was dichotomized to: 1) no symptoms, symptoms not bothersome, versus 2) symptoms bothersome or more severe, including symptoms interfering with daily activities.

[d] The asthma symptom severity score was dichotomized to: 1) no symptoms or symptoms not interfering with daily activities, versus 2) symptoms interfering with daily activities.

* $p < 0.05$; ** $p < 0.01$; † $p < 0.001$. NC = nonconvergence

Table 4.15. Relationship of asthma symptoms in children to concentrations of criteria pollutant gases measured at ambient outdoor central sites on days subjects gave VOC breath samples; Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Independent variable[a]	No. Obs.	Mean concentration (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[c]	Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[d]
O_3 1-hr max	77	25.5	0.60 (0.09, 3.87)	5.75 (3.52, 9.40)[†]
O_3 8-hr max	77	16.8	0.50 (0.08, 3.23)	4.74 (3.11, 7.23)[†]
NO_2 1-hr max	74	7.14	8.13 (1.52, 43.4)[*]	30.2 (11.3, 81.1)[†]
NO_2 8-hr max	74	5.99	7.14 (1.66, 30.7)[**]	16.9 (6.89, 41.6)[†]
SO_2 1-hr max	77	7.33	2.36 (1.16, 4.81)[*]	3.44 (2.46, 4.81)[†]
SO_2 8-hr max	77	4.97	1.91 (1.06 3.43)[*]	2.73 (2.10, 3.55)[†]
CO 1-hr max	77	7.23	1.22 (0.43, 3.43)	0.89 (0.60, 1.32)
CO 8-hr max	77	4.85	0.96 (0.27, 3.38)	0.67 (0.40, 1.13)

[a] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites. Mean values of pollutants are from the same day as symptom reports (lag 0) and from the subset of person-days (No. Obs.) when subjects gave exhaled breath samples for VOCs.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant, controlling for respiratory infections (2 subjects with invalid respiratory infection data are excluded). Models for bothersome or more severe asthma symptoms control for temperature as well.

[c] The asthma symptom severity score was dichotomized to: 1) no symptoms, symptoms not bothersome, versus 2) symptoms bothersome or more severe, including symptoms interfering with daily activities.

[d] The asthma symptom severity score was dichotomized to: 1) no symptoms or symptoms not interfering with daily activities, versus 2) symptoms interfering with daily activities.

[*] $p < 0.05$; [**] $p < 0.01$; [†] $p < 0.001$.

Table 4.16. Two-pollutant models for the relationship of asthma symptoms in children to concentrations of breath benzene controlling for ambient criteria pollutant gases; Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Independent variable[a]	Mean concentration	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[c]		Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[d]	
		Single pollutant	Two-pollutant	Single pollutant	Two-pollutant
Model 1:					
Breath Benzene	2.19 ng/L	2.03 (0.80, 5.11)	1.42 (0.60, 3.39)	2.56 (1.26, 5.21)**	3.49 (1.81, 6.71)†
O_3 1-hr max	25.5 ppb	0.60 (0.09, 3.87)	0.56 (0.09, 3.64)	5.75 (3.52, 9.40)†	6.54 (3.88, 11.0)†
Model 2:					
Breath Benzene	2.19 ng/L	2.03 (0.80, 5.11)	1.23 (0.50, 3.02)	2.56 (1.26, 5.21)**	2.32 (1.12, 4.82)*
NO_2 1-hr max	7.14 ppb	8.13 (1.52, 43.4)*	5.65 (0.85, 37.5)	30.2 (11.3, 81.1)†	42.9 (13.4, 137)†
Model 3:					
Breath Benzene	2.19 ng/L	2.03 (0.80, 5.11)	1.31 (0.55, 3.16)	2.56 (1.26, 5.21)**	2.18 (0.94, 5.05)
SO_2 1-hr max	7.33 ppb	2.36 (1.16, 4.81)*	1.98 (0.92, 4.25)	3.44 (2.46, 4.81)†	3.87 (2.54, 5.89)†

[a] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites. Mean values of pollutants are from the same day as symptom reports (lag 0) and from the subset of person-days (No. Obs.) when subjects gave exhaled breath samples for VOCs.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant, controlling for respiratory infections (2 subjects with invalid respiratory infection data are excluded). Models for bothersome or more severe asthma symptoms control for temperature as well.

[c] The asthma symptom severity score was dichotomized to: 1) no symptoms, symptoms not bothersome, versus 2) symptoms bothersome or more severe, including symptoms interfering with daily activities.

[d] The asthma symptom severity score was dichotomized to: 1) no symptoms or symptoms not interfering with daily activities, versus 2) symptoms interfering with daily activities.

* $p < 0.05$; ** $p < 0.01$; † $p < 0.001$.

4.3.5. Regression Analysis of Peak Expiratory Flow and VOC in Breath versus Ambient Air:
For multiple regression analyses of PEF we employed the general linear mixed model as described above. PEF maneuvers with reproducibility > 10% were excluded. Inclusion of these PEF observations made little difference in results though. The best fitting covariance structure by AIC was variance components. Models for morning and evening PEF were separately tested for confounding by: 1) temperature measured at the central sites; 2) respiratory tract infections; and 3) weekend. Maximum daily temperature was not associated with PEF ($p > 0.4$) and did not confound VOCs. PEF was not different on weekends compared with weekdays ($p > 0.6$) and did not confound VOCs. There was a significant inverse association between PEF and reports of respiratory infections, and parameters for the VOCs generally increased in models including respiratory infections. There were no significant interactions between respiratory infections and VOCs in mixed regression models ($p > 0.3$).

The effect of lag 0 respiratory infection was –34 L/min ($p < 0.01$) on morning PEF of the same day as the breath maneuver, and –44 L/min ($p < 0.002$) on evening PEF of the same day. For the following day's PEF (included in lag breath VOC models) the effect of a lag 1 respiratory infection was –15 L/min ($p < 0.3$) on morning PEF, and –26 L/min ($p < 0.14$) on evening PEF. The difference in statistical significance for lag 0 and lag 1 respiratory infection may have been due to the design of the study where subjects were instructed to collect breath samples on days with asthma exacerbations plus baseline symptom-free days. On the day of the canister sample, there were 10 respiratory infection reports, and on the following day there were 12 reports. However, only 8 out of 110 diaries (7%) stated that asthma symptoms were bothersome or worse on the day with breath benzene data lagged 1 day, in contrast to 18 out of 95 (19%) of such symptom reports on the same day with breath benzene data (lag day 0). As discussed, it is for this reason that analyses of lagged breath VOCs were not performed for symptoms above. However, it is possible that morning lung function deficits from previous exposures could still be detected on the day following the breath sample. Given that the breath samples were given toward the end of the day, morning PEF for the same day is less temporally relevant than morning PEF for the following day. Therefore, regression models are presented for evening PEF versus lag 0 breath VOCs, and for morning PEF versus lag 1 breath VOCs.

Table 4.17 shows results of mixed regression models for PEF versus breath VOC concentrations. These models are compared side-by-side with models for PEF versus the same ambient VOC concentrations. Reports of respiratory tract infections are controlled for in the models. Most models for breath VOCs showed no suggestion of an association (p-values > 0.2). A significant decrease in evening PEF of –29 L/min was found for a mean increase in breath tetrachloroethylene. There was no association with ambient tetrachloroethylene. A significant decrease in evening PEF of –21 L/min was found for a mean increase in ambient benzene. Borderline significant deficits in evening PEF were found in relation to ambient methylene chloride ($p < 0.08$) and ambient toluene ($p < 0.09$). Remaining models for ambient VOCs showed no suggestion of an association (p-values > 0.2).

Table 4.18 shows results of mixed regression models for PEF versus ambient criteria pollutant gas concentrations measured on the same day as the breath sample. A significant decrease in evening PEF of –13 L/min was found for a mean increase in ambient 1-hr SO_2. The association of 8-hr SO_2 with evening PEF was borderline significant ($p < 0.07$). There was also some suggestion of deficits in evening PEF with mean increases in 1-hr NO_2 ($p < 0.13$) and 8-hr CO ($p < 0.11$).

Table 4.17. The relationship of peak expiratory flow rates in asthmatic children to concentrations of volatile organic compounds measured in exhaled breath samples versus ambient outdoor central sites; Nov 1, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Dependent variable[a]	Independent variable[b]	No. obs.	Mean concentration (ng/L)	PEF change (95% CI)[c] per mean increase in VOC
AM PEF	Lag 1 Breath Benzene	80	2.19	-8.40 (-33.4, 16.6)
AM PEF	Lag 1 Ambient Benzene	70	5.67	-13.7 (-42.8, 15.3)
PM PEF	Lag 0 Breath Benzene	85		-9.95 (-27.6, 7.71)
PM PEF	Lag 0 Ambient Benzene	76		-21.4 (-39.1, -3.74)*
AM PEF	Lag 1 Breath p-Dichlorobenzene	75	36.3	-10.6 (-26.5, 5.29)
AM PEF	Lag 1 Ambient p-Dichlorobenzene	70	0.96	-4.23 (-27.4, 19.0)
PM PEF	Lag 0 Breath p-Dichlorobenzene	84		-4.30 (-15.5, 6.89)
PM PEF	Lag 0 Ambient p-Dichlorobenzene	76		-3.87 (-20.1, 12.4)
AM PEF	Lag 1 Breath Methylene Chloride	65	2.73	-3.49 (-32.2, 25.2)
AM PEF	Lag 1 Ambient Methylene Chloride	70	4.30	-0.81 (-21.1, 19.5)
PM PEF	Lag 0 Breath Methylene Chloride	62		-4.99 (-29.1, 19.1)
PM PEF	Lag 0 Ambient Methylene Chloride	76		-12.3 (-26.1, 1.45)
AM PEF	Lag 1 Breath Styrene	76	1.51	3.66 (-32.5, 39.9)
AM PEF	Lag 1 Ambient Styrene	70	0.51	2.09 (-15.4, 19.6)
PM PEF	Lag 0 Breath Styrene	84		12.8 (-12.1, 37.7)
PM PEF	Lag 0 Ambient Styrene	76		4.35 (-8.90, 17.6)
AM PEF	Lag 1 Breath Tetrachloroethylene	81	4.40	-8.00 (-34.0, 18.0)
AM PEF	Lag 1 Ambient Tetrachloroethylene	70	3.52	-7.64 (-30.1, 14.8)
PM PEF	Lag 0 Breath Tetrachloroethylene	87		-28.9 (-54.6, -3.23)*
PM PEF	Lag 0 Ambient Tetrachloroethylene	76		-0.69 (-16.2, 14.8)

Table 4.17. (continued)

Dependent variable	Independent variable	No. obs.	Mean concentration (ppb)	PEF change (95% CI) per mean increase in VOC
AM PEF	Lag 1 Breath Toluene	80	8.28	-8.83 (-41.5, 23.8)
AM PEF	Lag 1 Ambient Toluene	70	26.9	-16.0 (-41.8, 9.69)
PM PEF	Lag 0 Breath Toluene	84		-5.15 (-26.6, 16.3)
PM PEF	Lag 0 Ambient Toluene	76		-16.3 (-35.1, 2.47)
AM PEF	Lag 1 Breath m,p-Xylene	81	4.21	0.03 (-29.2, 29.3)
AM PEF	Lag 1 Ambient m,p-Xylene	70	13.3	-13.2 (-37.9, 11.4)
PM PEF	Lag 0 Breath m,p-Xylene	87		-1.10 (-21.6, 19.4)
PM PEF	Lag 0 Ambient m,p-Xylene	76		-10.6 (-27.9, 6.76)
AM PEF	Lag 1 Breath o-Xylene	81	1.47	2.48 (-20.1, 25.1)
AM PEF	Lag 1 Ambient o-Xylene	70	4.16	-13.6 (-37.2, 9.90)
PM PEF	Lag 0 Breath o-Xylene	85		-0.44 (-16.5, 15.6)
PM PEF	Lag 0 Ambient o-Xylene	76		-7.20 (-23.6, 9.22)

[a] Morning peak expiratory flow rate (AM PEF) and evening peak expiratory flow rate (PM PEF).

[b] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites. Pollutant concentrations are from the day previous to the morning PEF (lag 1) and from the same day (lag 0) as evening PEF. Mean values are from the untransformed concentrations for all VOC sample observations (person-days) in the mixed models. Breath VOCs are in ng/L and ambient VOCs are in ppb. Ambient observations are from the subset of person-days (No. Obs.) when subjects gave exhaled breath samples for VOCs.

[c] PEF change and 95% confidence intervals (CI) are from mixed linear regression models adjusting for respiratory infections, and estimate the lung function response for an mean change in air pollutant concentration. Mixed models for breath VOCs involved log-transformed concentrations.

[*] $p < 0.05$; [**] $p < 0.01$.

Table 4.18. The relationship of peak expiratory flow rates in asthmatic children to concentrations of criteria pollutant gases measured at ambient outdoor central sites when subjects gave exhaled breath samples for VOCs; Nov 1, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Dependent variable[a]	Independent variable[b]	No. obs.	Mean concentration (ppb)	PEF change (95% CI)[c] per mean increase in VOC
AM PEF	Lag 1 O_3 1-hr max	63	25.5	3.93 (-24.6, 32.5)
PM PEF	Lag 0 O_3 1-hr max	71		-1.28 (-21.4, 18.8)
AM PEF	Lag 1 O_3 8-hr max	63	16.8	1.00 (-26.3, 28.3)
PM PEF	Lag 0 O_3 8-hr max	71		0.48 (-18.6, 19.5)
AM PEF	Lag 1 NO_2 1-hr max	58	7.14	-10.3 (-57.7, 37.0)
PM PEF	Lag 0 NO_2 1-hr max	67		-25.7 (-58.6, 7.07)
AM PEF	Lag 1 NO_2 8-hr max	58	5.99	-13.3 (-59.7, 33.1)
PM PEF	Lag 0 NO_2 8-hr max	67		-22.2 (-55.2, 10.7)
AM PEF	Lag 1 SO_2 1-hr max	63	7.33	-0.83 (-18.5, 16.8)
PM PEF	Lag 0 SO_2 1-hr max	71		-13.2 (-25.9, -0.41)*
AM PEF	Lag 1 SO_2 8-hr max	63	4.97	-2.00 (-17.8, 13.8)
PM PEF	Lag 0 SO_2 8-hr max	71		-11.0 (-22.6, 0.54)
AM PEF	Lag 1 CO 1-hr max	63	7.23	-3.49 (-36.4, 29.4)
PM PEF	Lag 0 CO 1-hr max	71		-12.1 (-34.5, 10.4)
AM PEF	Lag 1 CO 8-hr max	63	4.85	-2.08 (-36.9, 32.7)
PM PEF	Lag 0 CO 8-hr max	71		-20.4 (-45.6, 4.71)

[a] Morning peak expiratory flow rate (AM PEF) and evening peak expiratory flow rate (PM PEF).

[b] The South Coast Air Quality Management District made ambient air pollution measurements at the stationary outdoor monitoring sites. Pollutant concentrations are from the day previous to the morning PEF (lag 1) and from the same day (lag 0) as evening PEF. Mean values of pollutants are from the same day as symptom reports (lag 0) and from the subset of person-days (No. Obs.) when subjects gave exhaled breath samples for VOCs.

[c] PEF change and 95% confidence intervals (CI) are from mixed linear regression models adjusting for respiratory infections, and estimate the lung function response for an mean change in air pollutant concentration.

- $p < 0.05$; ** $p < 0.01$.

Regression models were tested for the relationship of evening PEF to breath tetrachloroethylene or to ambient benzene, controlling for the criteria pollutant gases that were associated with the largest PEF deficits in Table 4.18 (1-hr NO_2, 1-hr SO_2, and 8-hr CO). The association between evening PEF and ambient benzene was not confounded by 1-hr NO_2. For a mean increase in benzene, this model showed a PEF deficit of –26.3 L/min (95% CI, –51.4, –1.30). This was a slightly larger deficit than the Table 4.17 model for benzene alone (–21.4 L/min). However, the regression parameter for 1-hr NO_2 flipped in the two-pollutant model compared with the single pollutant model in Table 4.18 and was nonsignificant (11.5 L/min, 95% CI, –30.4, 53.4). Ambient benzene was also not confounded by CO. Compared with the single pollutant models in Tables 4.17 and 4.18, the regression model for ambient benzene and 1-hr SO_2 showed associations for both pollutants were reduced: for benzene, –15.3 L/min, 95% CI, –38.5, 7.81; for 1-hr SO_2, –6.21 L/min, 95% CI, –21.7, 9.30.

The association between evening PEF and breath tetrachloroethylene was not confounded by 1-hr NO_2. For a mean increase in breath tetrachloroethylene, this model showed a PEF deficit of –28.3 L/min, 95% CI, –59.0, 2.43. This was similar to Table 4.17 model for tetrachloroethylene alone. Compared with the single pollutant model in Table 4.18, the regression parameter for 1-hr NO_2 was smaller and the CI wider in the two-pollutant model: –17.7 L/min, 95% CI, –51.9, 16.6. The regression model for breath tetrachloroethylene and 1-hr SO_2 showed little change in either pollutant's regression parameters compared with the single pollutant models. The regression model for breath tetrachloroethylene and 8-hr CO also showed little change in the regression parameter for tetrachloroethylene. However, compared with the single pollutant model the association with CO was reduced (–13.4 L/min, 95% CI, –40.2, 13.4).

In conclusion, two-pollutant models gave no evidence that ambient criteria pollutant gases confounded the significant associations with either ambient benzene or breath tetrachloroethylene. However, as with the two-pollutant models for symptoms, some problems of multicollinearity were suggested given the instability in both regression parameters along with inflation of variance for some models.

4.4. Analysis of Effects of Personal VOC Exposures

4.4.1. Asthma Symptoms Among Subjects Wearing Personal VOC Badge:

Symptoms during the 23-33 days of personal VOC exposure assessment are shown by subject in Table 4.19. One of the four subjects (2473) had no symptoms, another subject (2469) reported only 2 out of 23 days with symptoms that were not bothersome, and another (2497) had just one day with symptoms that interfered with daily activities. Only one subject had frequent symptoms (2474). Because of the sparseness of clinically relevant symptom occurrences in all but one subject, an analysis of the relationship between symptoms and personal VOC exposure will not be presented. An analysis of the continuous variable PEF is not limited in this manner and will be presented below.

Table 4.19. Frequency of symptom scores in four subjects participating in the VOC personal exposure assessment, Asthma Panel Study, Huntington Park region.

	Subject ID			
Symptom score (column %)	2469	2473	2474	2497
None	21 (91.3)	32 (100)	7 (23.3)	28 (84.9)
Very Mild	2 (8.7)	0 (0)	14 (46.7)	3 (9.1)
Mild	0 (0)	0 (0)	7 (23.3)	1 (3.0)
Moderate	0 (0)	0 (0)	2 (6.7)	0 (0)
Severe	0 (0)	0 (0)	0 (0)	1 (3.0)
Total observation days	23	32	30	33

4.4.2. Regression Analysis of Peak Expiratory Flow and VOC Badge Data:

For multiple regression analyses of PEF in relation to personal VOC exposures we employed the general linear mixed model using the SAS procedure Mixed as described above. When PEF maneuvers with reproducibility > 10% were excluded, standard errors increased. This may have occurred because the highest 1 of 3 maneuvers was valid in this group of 4 subjects considered to be highly compliant with procedures. Also, the sample size was limited (116 to 122 person-days). Therefore, all PEF maneuvers were retained for analysis. Regression models were examined separately for morning and evening PEF. Evening PEF was examined in relation to personal VOC concentrations on the day subjects performed the maneuver, i.e., the day of the badge sample (lag 0). Morning PEF was examined in relation to personal VOC concentrations on the day before subjects performed the PEF maneuver (lag 1) to maintain the appropriate temporal relationship. Models were separately tested for confounding by: 1) temperature measured at the central sites; 2) respiratory tract infections; and 3) weekend. An autoregressive parameter was needed to adjust for autocorrelated error terms.

Temperature lag 1 day was not significantly associated with morning PEF (+0.88 L/min per °F, $p < 0.19$). Weekend was not significantly associated with either morning PEF ($p > 0.4$) or evening PEF ($p > 0.7$). The relationship of lag 0 maximum temperature with evening PEF was also not significant (–0.85 L/min per °F, $p < 0.14$). Temperature did not confound parameters for any personal VOC compound in relation to evening PEF. Controlling for lag 1 temperature changed parameters for personal VOC compounds by around 10-15% in models for morning PEF, but temperature was not significant in the models ($p > 0.4$). Therefore, temperature was not included in final models.

There was a significant inverse association between evening PEF and 7 reports of respiratory infections on the same day (–38.0 L/min, $p < 0.01$). Although nonsignificant, the regression parameter for lag 0 respiratory infections was negative as well in relation to morning PEF (–15.8 L/min, $p < 0.29$). The effect of lag 1 respiratory infection on morning PEF was larger: –22.0 L/min ($p < 0.12$). Parameters for the VOCs generally became more negative (higher VOC, lower PEF) in models for evening PEF including respiratory infections. However, parameters for the VOCs generally became more positive in models for morning PEF including lag 1 respiratory infections. Model fit for morning and evening PEF also improved controlling for respiratory infections. There were no significant interactions between respiratory infections and VOCs in mixed regression models ($p > 0.3$).

Table 4.20 shows results of multivariate models for morning or evening PEF versus lag 0 or versus lag 1 day personal. Models for ambient VOCs are given after each model for the same personal VOC variable. Morning PEF models control for lag 1 respiratory infections, and evening PEF models control for lag 0 respiratory infections. Changes in PEF are given at the mean VOC concentration.

Table 4.20. Relationship between peak expiratory flow rates in 4 asthmatic children to concentrations of volatile organic compounds measured by personal passive samplers versus ambient outdoor central sites, Huntington Park region, Los Angeles County, California.

Dependent Variable[a]	Independent Variable and Lag day (0 = current, 1 = day prior to PEF maneuver)	Arithmetic Mean (SD) (ng/L)[b]	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 Personal Benzene	12.7 (9.37)	2.26 (-28.0, 32.5)
	Lag 1 Ambient Benzene		-4.94 (-16.9, 7.05)
PM PEF	Lag 0 Personal Benzene		-4.27 (-26.8, 18.2)
	Lag 0 Ambient Benzene		-1.99 (-12.9, 8.91)
PM PEF	Lag 1 Personal Benzene		7.91 (-18.0, 33.9)
	Lag 1 Ambient Benzene		9.92 (-0.68, 20.5)
AM PEF	Lag 1 Personal p-Dichlorobenzene	6.76 (9.37)	-13.7 (-36.7, 9.33)
	Lag 1 Ambient p-Dichlorobenzene		-1.29 (-10.3, 7.76)
PM PEF	Lag 0 Personal p-Dichlorobenzene		-20.5 (-40.5, -0.42)*
	Lag 0 Ambient p-Dichlorobenzene		-3.68 (-11.9, 4.52)
PM PEF	Lag 1 Personal p-Dichlorobenzene		-16.9 (-37.9, 4.11)
	Lag 1 Ambient p-Dichlorobenzene		0.09 (-8.13, 8.32)
AM PEF	Lag 1 Personal Styrene	5.87 (3.40)	-18.6 (-43.2, 6.04)
	Lag 1 Ambient Styrene		-4.59 (-14.5, 5.32)
PM PEF	Lag 0 Personal Styrene		-15.9 (-34.5, 2.70)
	Lag 0 Ambient Styrene		-6.05 (-14.4, 2.30)
PM PEF	Lag 1 Personal Styrene		-13.4 (-32.4, 5.65)
	Lag 1 Ambient Styrene		3.07 (-5.82, 12.0)
AM PEF	Lag 1 Personal Toluene	56.6 (33.3)	-4.83 (-58.3, 48.6)
	Lag 1 Ambient Toluene		-9.45 (-22.3, 3.44)
PM PEF	Lag 0 Personal Toluene		-5.30 (-46.6, 36.0)
	Lag 0 Ambient Toluene		-10.2 (-21.7, 1.32)
PM PEF	Lag 1 Personal Toluene		10.2 (-35.7, 56.1)
	Lag 1 Ambient Toluene		2.91 (-8.70, 14.5)

Table 4.20. (continued)

Dependent Variable[a]	Independent Variable and Lag day (0 = current, 1 = day prior to PEF maneuver)	Arithmetic Mean (SD) (ng/L)[b]	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 Personal Tetrachloroethylene	5.87 (5.24)	-6.91 (-23.3, 9.51)
	Lag 1 Ambient Tetrachloroethylene		-5.45 (-16.7, 5.77)
PM PEF	Lag 0 Personal Tetrachloroethylene		-8.20 (-20.6, 4.20)
	Lag 0 Ambient Tetrachloroethylene		-12.1 (-22.3, -1.92)*
PM PEF	Lag 1 Personal Tetrachloroethylene		-5.81 (-18.8, 7.18)
	Lag 1 Ambient Tetrachloroethylene		2.12 (-8.41, 12.7)
AM PEF	Lag 1 Personal m,p-Xylene	55.6 (33.6)	-19.8 (-75.3, 35.7)
	Lag 1 Ambient m,p-Xylene		-6.61 (-19.3, 6.08)
PM PEF	Lag 0 Personal m,p-Xylene		-36.9 (-79.8, 5.88)
	Lag 0 Ambient m,p-Xylene		-12.8 (-24.1, -1.56)*
PM PEF	Lag 1 Personal m,p-Xylene		-31.9 (-77.9, 14.0)
	Lag 1 Ambient m,p-Xylene		4.27 (-6.96, 15.5)
AM PEF	Lag 1 Personal o-Xylene	12.8 (7.44)	-20.4 (-56.7, 16.0)
	Lag 1 Ambient o-Xylene		-5.95 (-17.7, 5.75)
PM PEF	Lag 0 Personal o-Xylene		-28.9 (-56.4, -1.35)*
	Lag 0 Ambient o-Xylene		-10.1 (-20.5, 0.32)
PM PEF	Lag 1 Personal o-Xylene		-29.0 (-57.5, -0.56)*
	Lag 1 Ambient o-Xylene		3.99 (-6.52, 14.5)

* $p<0.05$; ** $p< 0.01$

[a] Morning peak expiratory flow rate (AM PEF), with 122 observations with personal VOC exposures, 118 for ambient VOC, and evening peak expiratory flow rate (PM PEF), with 116 observations with personal VOC exposures and 116 for ambient VOC.

[b] This is the untransformed concentration for all sample observations in the mixed models.

[c] PEF Change and 95% Confidence Intervals (CI) are from mixed linear regression models adjusting for respiratory infections, and estimate the lung function response for a mean concentration change in log transformed personal VOC from the passive badge sampler.

There were no significant associations for morning PEF in relation to either personal or ambient VOCs. Significant decreases in evening PEF were found in relation to personal exposure to lag 0 *p*-dichlorobenzene, to lag 0 *o*-xylene and to lag 1 *o*-xylene (Table 4.20). Borderline significant decreases in evening PEF were found in relation to personal exposure to lag 1 *p*-dichlorobenzene, lag 0 styrene and lag

0 *m,p*-xylene. Significant decreases in evening PEF were found in relation to ambient exposure to lag 0 tetrachloroethylene and *m,p*-xylene. Borderline significant decreases in evening PEF were also found in relation to ambient exposure to lag 0 toluene, lag 0 *o*-xylene. Among these findings, the only consistent associations for evening PEF in relation to both personal and ambient exposures were for lag 0 *o*-xylene and lag 0 *m,p*-xylene.

In conclusion, personal VOC exposures were more strongly associated with PEF deficits than ambient VOC exposures. Overall results for personal VOCs show that regression parameters were negative for 18 out of 21 models (86%), with 12 being –10 L/min or less (57%) for a mean increase in VOC. In comparison, overall results for ambient VOCs show that regression parameters were negative for 14 total of out of 21 models (67%), with only 4 being –10 L/min or less (19%) for a mean increase in VOC. For 4 subjects wearing personal samplers, six models were significant or nearly so for evening PEF in relation to personal exposures to *p*-dichlorobenzene, styrene, *m,p*-xylene and *o*-xylene.

Table 4.21 shows results of mixed regression models for PEF versus ambient criteria pollutant gas concentrations during the personal exposure study. There were no significant PEF deficits in relation to criteria pollutant gases. Nevertheless, overall results show that regression parameters were negative for 16 out of 24 models (67%). Borderline significant decreases in morning PEF were found in relation to lag 1 8-hr CO. Borderline significant decreases in evening PEF were also found in relation to lag 0 SO_2, lag 0 1-hr CO, as well as lag 0 and lag 1 8-hr CO. Ozone was positively and significantly associated with PEF in two models. This is not expected to be a causal association.

Table 4.21. The relationship of daily peak expiratory flow rates in 4 asthmatic children to concentrations of criteria pollutant gases; Huntington Park region, Los Angeles County, California.

Dependent Variable[a]	Independent Variable[b]	Mean Concentration (ppb)	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 O_3 1-hr max	25	10.5 (-6.74, 27.8)
PM PEF	Lag 0 O_3 1-hr max		16.4 (1.47, 31.4)*
PM PEF	Lag 1 O_3 1-hr max		-4.96 (-19.7, 9.81)
AM PEF	Lag 1 O_3 8-hr max	17	16.3 (-0.36, 33.0)
PM PEF	Lag 0 O_3 8-hr max		15.9 (1.02, 30.8) *
PM PEF	Lag 1 O_3 8-hr max		-4.98 (-18.8, 8.83)
AM PEF	Lag 1 NO_2 1-hr max	7	3.75 (-14.4, 22.0)
PM PEF	Lag 0 NO_2 1-hr max		-12.7 (-31.6, 6.18)
PM PEF	Lag 1 NO_2 1-hr max		-1.46 (-19.6, 16.7)
AM PEF	Lag 1 NO_2 8-hr max	6	-2.83 (-27.1, 21.4)
PM PEF	Lag 0 NO_2 8-hr max		-17.9 (-42.2, 6.44)
PM PEF	Lag 1 NO_2 8-hr max		1.38 (-22.4, 25.1)

Table 4.21. (continued)

Dependent Variable[a]	Independent Variable[b]	Mean Concentration (ppb)	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 SO_2 1-hr max	7	-3.67 (-18.6, 11.2)
PM PEF	Lag 0 SO_2 1-hr max		-11.5 (-24.7, 1.58)
PM PEF	Lag 1 SO_2 1-hr max		4.16 (-8.41, 16.7)
AM PEF	Lag 1 SO_2 8-hr max	5	-4.19 (-21.2, 12.8)
PM PEF	Lag 0 SO_2 8-hr max		-9.57 (-24.7, 5.52)
PM PEF	Lag 1 SO_2 8-hr max		0.75 (-13.4, 14.9)
AM PEF	Lag 1 CO 1-hr max	8	-7.18 (-27.2, 12.8)
PM PEF	Lag 0 CO 1-hr max		-14.7 (-31.6, 2.27)
PM PEF	Lag 1 CO 1-hr max		-7.27 (-24.0, 9.46)
AM PEF	Lag 1 CO 8-hr max	5	-16.7 (-37.1, 3.70)
PM PEF	Lag 0 CO 8-hr max		-14.0 (-30.9, 2.86)
PM PEF	Lag 1 CO 8-hr max		-14.4 (-31.8, 3.06)

[a] Morning peak expiratory flow rate (AM PEF) and evening peak expiratory flow rate (PM PEF).

[b] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites. Pollutant concentrations are from the day previous to the morning PEF (lag 1) and from the same day (lag 0) as evening PEF.

[c] PEF Change and 95% Confidence Intervals (CI) are from mixed linear regression models adjusting for respiratory infections, and estimate the lung function response for an mean change in air pollutant concentration.

[*] $p < 0.05$; [**] $p < 0.01$.

4.5. Analysis of Effects of Daily Ambient Air Pollution Throughout the Panel Follow-up

4.5.1. Descriptive Analysis of Asthma Severity:

Table 4.22 shows the overall characteristics of subjects for the entire panel period. The table includes data for the 22 subjects included in single pollutant univariate regression analyses, excluding data for IDs 2484 and 2487. As discussed above, data for these two subjects led to an inflation of standard errors in regression models. The panel is described in Table 4.22 by the number of days that subjects had episodes of asthma when symptoms interfered with daily activities (score > 2). Only 7 subjects reported asthma symptoms that interfered with daily activities (symptom scores > 2). We also used daily symptom reports to classify a subject's asthma severity in a manner consistent with the National Heart Lung and Blood Institute (NHLBI) symptom-based criteria (NHLBI, 1997), irrespective of asthma medication regimen. Only five subjects had mild persistent or more severe asthma, defined as having daily diary reports of any asthma symptoms (score > 0) on more than 2 times a week throughout the study. The remaining

seventeen subjects were considered to have mild intermittent asthma based on symptom frequency alone. Five of these subjects were asymptomatic, and one other had no asthma symptom scores over 1 (i.e., no bothersome or more severe symptoms). There were no subjects with continuous asthma symptoms consistent with NHLBI severe persistent asthma.

Lung function tests for FEV_1 and FVC are shown for each subject in Table 4.23. Technicians administered the tests at the beginning and end of the study. Percent predicted FEV_1 are shown in the table and are from prediction equations for Hispanic children in Hankinson et al. (1999). It is used as an alternate definition of asthma severity (NHLBI, 1997). Only four subjects had both asthma symptoms more than 2 times per week on average or > 28% of days (mild persistent or worse, irrespective of asthma medication regimen) and < 80% predicted FEV_1 (moderate persistent by NHLBI criteria) at either pre- or post-study spirometry session: 2474, 2491, 2497, and 2501 (Table 4.23). Two of these subjects had consistently low percent-predicted FEV_1 across two maneuvers (2491 and 2497). Subject 2469 also had consistently low percent-predicted FEV_1 across two maneuvers (< 0.75%) and was symptomatic on 16% of observed days. Subject 2501 had very inconsistent percent-predicted FEV_1 across pre- and post-study spirometry sessions, and 2474 had a modest difference. Another subject was symptomatic on 19% of observed days and had a post-study percent predicted FEV_1 of 0.68 versus a pre-study percent predicted FEV_1 of 0.84. These 6 subjects were among the 7 subjects who reported asthma that interfered with daily activities (symptom scores > 2). For the purpose of examining symptom responses to air pollutants, these six subjects could be viewed as the "more severe" asthmatics with regard to their experience of asthma symptoms during the study and predicted FEV_1: 2469, 2474, 2488, 2491, 2497, and 2501. This classification is consistent with the definition of persistent asthma by NHLBI criteria.

Eight other subjects showed one or both of pre- post-maneuvers to have FEV_1 < 80% predicted, but did not have persistent asthma by symptoms, irrespective of asthma medication regimen. Four had FEV_1/FVC ratios < 0.75 at the maneuver with a low percent-predicted FEV_1. For instance, although 2468 had percent predicted FEV_1 < 0.80, he was virtually asymptomatic, suggesting either poor perception of asthma status or inappropriate percent predicted FEV_1. However, the ratio of FEV_1/FVC was around 0.6, suggesting an obstructive deficit. Therefore, although these may have been asthmatics with persistent asthma by lung function, for the purpose of the symptom-based analysis, they were less severe than the six described above. We choose to refer to these 16 subjects as having "less severe" asthma. Two of these subjects were those with invalid respiratory infection data. This classification of more severe versus less severe will be used below as an exploratory test of whether relationships between ambient pollutants and symptoms differ between the groups.

Table 4.22. Descriptive statistics for 22 asthmatic children in analysis of daily diary data, Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Subject characteristic	
Median age (age Range)	12 (10-16)
No. males / females	18 / 4
No. days asthma symptoms interfered with daily activities / person-days (%)	26 / 1,123 (2.3%)
No. days asthma symptoms were bothersome or worse / person-days (%)	79 / 1,123 (7.0%)
No. subjects with mild persistent or more severe asthma[a]	5 (23%)
No. subjects with percent predicted FEV_1 < 80% at panel beginning and end	5 (23%)
No. subjects taking regularly scheduled anti-inflammatory medications	6 (27%)
Mean daily as-needed β-agonist inhaler puffs (SD)	1.32 (1.79)

[a] defined as daily diary reports of symptoms on > 2 times a week throughout the study (NHLBI, 1997), irrespective of asthma medication regimen. Days examined are those when ambient measurements of air pollutants were available.

Table 4.23. Lung function at baseline and at the end of the panel study for 22 asthmatic children, Huntington Park region, Los Angeles County, California.

ID	Baseline FVC	Baseline FEV_1	End of Study FVC	End of Study FEV_1	Baseline Percent Predicted FEV_1[a]	End of Study Percent Predicted FEV_1
2468	3.24	1.97	2.77	1.50	0.72	0.55
2469	1.85	1.48	1.96	1.57	0.69	0.74
2470	3.91	3.78	3.70	3.36	1.07	0.95
2472	2.12	1.90	2.48	2.10	0.76	0.84
2473	4.22	3.62	4.16	3.06	0.92	0.78
2474	2.63	1.93	2.84	2.09	0.78	0.84
2483	2.78	2.34	2.73	2.27	1.05	1.02
2485	3.23	3.18	3.82	3.28	0.86	0.89
2486	2.96	2.76	3.05	2.79	1.00	1.01
2488	4.03	3.27	3.86	2.63	0.84	0.68
2489	3.29	2.92	3.76	3.19	0.84	0.92
2490	3.53	2.94	3.75	3.01	0.86	0.88
2491	2.74	2.04	2.95	2.04	0.71	0.71
2492	2.39	1.67	3.42	3.00	0.57	1.03
2494	1.87	1.57	1.95	1.75	0.76	0.84
2495	2.82	2.57	3.16	2.44	0.73	0.69
2496	3.00	2.70	3.31	2.98	0.93	1.03
2497	1.96	1.04	2.66	1.66	0.40	0.63
2498	1.89	1.72	2.27	1.88	0.75	0.82
2499	2.06	1.85	2.20	1.93	0.79	0.82
2500	3.00	2.86	4.30	3.06	0.87	0.93
2501	2.68	2.43	3.41	3.15	0.77	1.00

[a] Predicted FEV_1 are from prediction equations for Hispanic children in Hankinson et al., 1999.

We will also test whether regression parameter estimates for ambient pollutants differ between subjects taking versus not taking anti-inflammatory medications. However, only six subjects were taking anti-inflammatory medications regularly, therefore, this analysis should be also considered exploratory because of limited sample size in this group. Among these six subjects, three (50%) experienced asthma episode days with symptom scores > 2, and two (33%) fit the NHLBI classification of persistent asthma by symptom frequency (not shown in Table). Among the sixteen subjects not taking anti-inflammatory medications, four (25%) experienced any asthma episode days and three (19%) fit the NHLBI classification of persistent asthma. GEE models were tested for medication group predicting the binary

symptom outcome. Subjects taking anti-inflammatory medications were two times more likely to have bothersome or more severe asthma symptoms, but this was not significant (p = 0.18). However, subjects taking anti-inflammatory medications were not more likely to have symptom interfering with daily activities (p = 0.85).

4.5.2. Descriptive Analysis of Ambient Exposures:

Table 4.24 shows descriptive data for the ambient exposures across the three months of study, Nov. 4, 1999 through Jan. 23, 2000. As with the subset of days when subjects gave breath samples (Table 4.9), none of the observed days exceeded the U.S. NAAQS for criteria air pollutant gases. The VOC levels are typical of the time period and region of study, and represent relatively high ambient levels on many days (SCAQMD, 2000). For instance, the 90th percentile of benzene was 2.90 ppb and for toluene was 12.40 ppb. Ambient formaldehyde was relatively low (maximum 14 ppb) compared with indoor levels that have been associated with respiratory or allergic outcomes (discussed above). Particle mass and EC-OC data are shown in Table 4.25 for the subset of available days. Mass concentrations of PM_{10} (gravimetric or TEOM) never exceeded the U. S. NAAQS of 150 μ/m^3 for 24 hour averages, although several days approached the standard. We give ambient VOC concentrations here in ppb. Conversions to ng/L from ppb are: 3.18776 (Benzene), 3.46531 (Methylene Chloride), 4.25306 (Styrene), 6.76735 (Tetrachloroethylene), 3.75918 (Toluene), 4.33469 (m,p-Xylene), 4.33469 (o-Xylene), 6.0000 (p_Dichlorobenzene).

Table 4.24. Daily air pollution measurements, Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Exposure & averaging time[a]	No. obs.	Mean (SD)	Minimum / Maximum	90th Percentile
O_3 1-hr max (ppb)	74	25 (10)	4 / 52	38
O_3 8-hr max (ppb)	74	17 (7)	3 / 37	26
NO_2 1-hr max (ppb)[b]	69	7 (2)	3 / 14	9
NO_2 8-hr max (ppb)[b]	69	6 (2)	3 / 11	8
SO_2 1-hr max (ppb)	74	7 (4)	2 / 26	11
SO_2 8-hr max (ppb)	74	5 (3)	1 / 20	7
CO 1-hr max (ppb)	74	8 (3)	2 / 17	12
CO 8-hr max (ppb)	74	5 (2)	1 / 10	8
Acetaldehyde (ppb)[b]	69	3.11 (1.00)	1.05 / 5.79	4.55
Acetone (ppb)[b]	69	7.11 (3.74)	1.64 / 17.12	12.32
Formaldehyde (ppb)[b]	69	7.21 (2.41)	4.27 / 14.02	10.09
Benzene (ppb)	74	1.82 (0.79)	0.03 / 4.30	2.90

Table 4.24. (continued)

Exposure & averaging time[a]	No. obs.	Mean (SD)	Minimum / Maximum	90th Percentile
1,3-Butadiene (ppb)	74	0.51 (0.28)	0.05 / 1.50	1.00
Chloromethane (ppb)	73	0.58 (0.14)	0.40 / 1.10	0.70
p_Dichlorobenzene (ppb) [c]	74	0.15 (0.09)	0.05 / 0.50	0.30
Ethylbenzene (ppb)	74	0.59 (0.36)	0.05 / 2.20	1.10
Methylene Chloride (ppb)	74	1.22 (0.86)	0.30 / 4.70	2.40
Styrene (ppb) [c]	74	0.10 (0.07)	0.05 / 0.40	0.20
Tetrachloroethylene (ppb)	74	0.51 (0.28)	0.05 / 1.40	0.90
Toluene (ppb)	74	7.17 (3.49)	1.90 / 19.40	12.40
m,p-Xylene (ppb)	74	3.07 (1.61)	0.30 / 9.10	4.80
o-Xylene (ppb)	74	0.94 (0.53)	0.10 / 3.00	1.60
Temperature 1-hr max (°F)	80	71 (6)	50 / 82	79

[a] Exposure measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites. There was no VOC monitoring Dec 25 through 26, and Dec 31 through Jan 4. Monitoring of criteria gases began Nov 11.

[b] Fewer days of observation was due to sampling or deployment problems.

[c] Many days for styrene (37) and p-dichlorobenzene (21) were below the method detection limit (MDL); for these days, values were set at half the MDL.

Table 4.25. Daily particulate air pollution measurements. Subset of days Nov 4 through Dec 28, 1999, Huntington Park region, Los Angeles County, California.

Exposure & Averaging Time[a]	No. Obs.	Mean (SD)	Minimum / Maximum	90th Percentile
Nov 4 – 26, Dec 8 and 14 1999:				
Gravimetric PM_{10} 24-hr mean ($\mu g/m^3$)	24	60 (25)	20 / 126	86
Elemental Carbon 24-hr mean ($\mu g/m^3$)	24	5.09 (1.86)	1.79 / 9.42	7.36
Organic Carbon 24-hr mean ($\mu g/m^3$)	24	9.47 (3.08)	4.29 / 17.05	13.03
Dec 19 – 28, 1999:				
TEOM PM_{10} 1-hr max ($\mu g/m^3$)	10	92 (24)	56 / 132	123
TEOM PM_{10} 8-hr max ($\mu g/m^3$)	10	64 (19)	35 / 87	86
TEOM PM_{10} 24-hr mean ($\mu g/m^3$)	10	52 (18)	25 / 77	74

[a] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites. Samplers for particle mass and carbon were operated only on a subset of days during the panel study.

Figures 4-13 show time plots of the various pollutants. The time plots for VOCs are plotted against 8-hr NO_2 to give a point of reference to a potentially important criteria air pollutant gas with respect to asthma. NO_2 is widely monitored in urban areas, an important pollutant gas in heavy traffic areas such as southern California, and may play a causal role in asthma and/or act as a surrogate for more causal combustion-related pollutants. A moderately strong correlation of NO_2 with the VOCs is clearly demonstrated in the time plots. A time plot of gravimetric PM_{10} with EC and OC is also shown.

Table 4.26 shows a Spearman rank correlation matrix for selected ambient air pollutants. There were moderate correlations between criteria air pollutant gases other than O_3 (NO_2, CO, SO_2) and several VOCs, including acetaldehyde, formaldehyde, toluene and *m,p*-xylene. This is graphically shown with time plots for NO_2 and selected VOCs in Figures 4.4-4.5 and 4.7. Acetone was weakly, but significantly correlated with NO_2 (see time plot Figure 4.6) and with O_3. The above positive correlations likely represent common sources from fossil fuel combustion and/or common meteorological determinants such as air stagnation. This correlation can influence the ability to fit regression models that include the two pollutant types. The VOCs showed moderate to strong correlations between them. Also, NO_2 and SO_2 were strongly correlated (see time plot Figure 4.9). Generally, all pollutants were positively correlated with temperature and negatively correlated with wind speed, which would be expected to clear some locally generated pollutants. The exception was with O_3, which was positively correlated with wind speed, suggesting some importance of transport from other regions and/or decreased neutralization by local NO with increased wind speed. Ozone was not correlated with NO_2 (see time plot Figure 4.8).

Table 4.26. Outdoor air pollution and weather correlation matrix,[a] Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

	8-hr max. O_3	8-hr max. CO	8-hr max. SO_2	Acet-aldehyde	Acetone	Form-aldehyde	Benzene	Ethyl-benzene	Tetra-chloro-ethylene	Toluene	m,p-Xylene	8-hr max. Temp	8-hr max. Wind Speed
8-hr max. NO_2	-0.20	0.65†	0.89†	0.69†	0.29*	0.57†	0.57†	0.66†	0.65†	0.70†	0.72†	0.32**	-0.21
8-hr max. O_3		-0.17	-0.19	-0.22	0.33**	0.09	0.03	-0.12	-0.13	-0.15	-0.08	0.11	0.36**
8-hr max. CO			0.69†	0.51†	0.28*	0.41†	0.50†	0.62†	0.63†	0.71†	0.72†	0.41†	-.33**
8-hr max. SO_2				0.54†	0.31*	0.39**	0.59†	0.63†	0.62†	0.69†	0.72†	0.43†	-0.26*
Acetaldehyde					0.28*	0.79†	0.50†	0.63†	0.52†	0.68†	0.65†	0.34**	-0.25*
Acetone						0.59†	0.27*	0.37**	0.46†	0.37**	0.42†	0.41†	-0.01
Formaldehyde							0.38**	0.50†	0.40†	0.52†	0.52†	0.44†	0.05
Benzene								0.71†	0.62†	0.75†	0.79†	0.24*	-0.07
Ethylbenzene									0.84†	0.90†	0.94†	0.30**	-0.24*
Tetrachloroethylene										0.87†	0.85†	0.40†	-0.24*
Toluene											096†	0.43†	-0.32**
m,p-Xylene												0.35**	-0.29*
8-hr max. Temp													-0.05

[a] Spearman correlation coefficients (p-value); The number of observations is 74 for SO_2, CO, O_3, weather, and VOCs and 69 for NO_2 and carbonyls.

* $p < 0.05$; ** $p < 0.01$; † $p < 0.001$;

Spearman rank correlations between gravimetric PM_{10}, EC, OC, and VOCs were also examined (not shown). Only 12-17 out of 24 days overlapped for both gravimetric data and criteria gases. Gravimetric PM_{10} was strongly correlated with EC and OC (r = 0.82 and 0.81, respectively) as graphically shown with time plots in Figures 4.12 and 4.13. Gravimetric PM_{10} moderately correlated with most of the VOCs (r = 0.50 to 0.66) and weakly correlated with acetone (r = 0.32). Gravimetric PM_{10} was not correlated with formaldehyde (r = –0.1). EC and OC were both moderately correlated with most of the VOCs (r = 0.60 to 0.78) as shown for *m,p*-xylene in Figures 4.11 and 4.12. EC and OC were weakly correlated with acetaldehyde (r = 0.36), and not correlated with formaldehyde (r = –0.1).

4.5.3. Regression Analysis of Asthma Symptoms and Ambient Air Pollutants:

4.5.3.1. Lag pollutant models for symptom scores > 1:
Regression models were tested for the relationship of symptom scores > 1 and pollutants measured on previous days. There were no significant associations for lag 1 or 2 days for any non-carbonyl VOC or criteria air pollutant gas, but several compounds were borderline significant ($p < 0.1$) at lag 1 day (1-hr NO_2, OR 2.00, and 1,3-butadiene, OR 1.59), and at lag 2 days (styrene, OR 1.24). There were no associations with asthma symptoms at lag 3 days. At lag 4 days, only CO was significantly associated with symptom scores > 1 (OR 2.43). A borderline significant relationship was found for 4-day lag 1,3-butadiene, OR of 1.38 ($p = 0.08$).

There were significant associations of asthma symptom scores > 1 with carbonyl compounds at lag 1 day for acetaldehyde, OR 2.51 (95% CI, 1.42, 4.42) and formaldehyde, OR 2.64 (95% CI, 1.12, 6.21). Lag 4 formaldehyde also showed an OR of 1.60 ($p = 0.12$). Recall that lag 0 carbonyl compounds were not associated with asthma symptom scores > 1.

Lags were then combined with lag 0 to form multi-day moving averages. Two-day moving averages of NO_2 and SO_2 were associated with symptom scores > 1: 8-hr NO_2, OR 2.73 (95% CI, 1.06, 7.03); 8-hr SO_2, OR 1.52 (95% CI, 1.14, 2.05). Several of the 2-day moving averages for non-carbonyl VOCs were significant or borderline significant with ORs between 1.5 and 2.0, including benzene, ethylbenzene, 1,3-butadiene, *m,p*-xylene and *o*-xylene. Four-day moving averages of non-carbonyl VOCs and criteria air pollutant gases were not significantly associated with symptoms, likely due to attenuation of associations by lags > 1 day.

Significant associations with symptom scores > 1 were found for 2-day moving averages of acetaldehyde (OR 3.35, 95% CI, 1.07, 10.5). Four-day moving averages for acetaldehyde were not significant but the ORs were elevated (OR 3.19, $p < 0.14$).

4.5.3.2. Lag pollutant models for symptom scores > 2:
Few of the non-carbonyl VOC or criteria air pollutant gases were significantly associated with symptom scores > 2. Symptoms were only significantly associated with lag 2 styrene, OR 2.18 (95% CI, 1.47, 3.24) and lag 3 styrene, OR 1.71 (95% CI, 1.16, 2.52) and lag 4 *p*-dichlorobenzene, OR 2.17 (95% CI, 1.45, 3.23).

There were significant associations of asthma symptom scores > 2 and carbonyl compounds: lag 1 day acetone, OR 2.23 (95% CI, 1.19, 4.20), lag 4 acetaldehyde, OR 4.79 (95% CI, 1.78, 12.9), and lag 4 formaldehyde, OR 5.56 (95% CI, 1.88, 16.5). Other lags for carbonyl compounds were also not significant but the OR were elevated: Lag 2 acetone, OR 1.81 (95% CI, 0.82, 4.03; $p<0.16$) lag 2 acetaldehyde, OR 2.09 (95% CI, 0.72, 6.05; $p < 0.18$) and lag 2 formaldehyde, OR 3.42 (95% CI, 0.67, 17.3; $p<0.14$). Dropping the one influential subject with high symptom responses discussed above had

little effect on lag 1 and 4, with small reductions in the OR for lag 1 acetone to 1.91 and lag 4 acetaldehyde to 3.96, but reduced ORs to nearly 1.0 for lag 2.

Again, lags were then combined with lag 0 to form multi-day moving averages. Two-day moving averages of NO_2 and SO_2 were associated with symptom scores > 2: 8-hr NO_2, OR 5.03 (95% CI, 1.12, 22.6) and 8-hr SO_2, OR 1.94 (95% CI, 1.36, 2.76). However, these associations were lost dropping the most symptomatic subject discussed above. Symptoms were significantly associated with 2-day moving averages of styrene OR 2.41 (95% CI, 1.40, 4.15) and 4-day moving averages of styrene OR 2.78 (95% CI, 1.51, 5.10). Dropping the most symptomatic subject reduced the OR to 1.77 for 2-day and 2.18 for 4-day averages.

Significant associations were found for 2-day moving averages of acetone (OR 3.21, 95% CI, 1.18, 8.73) and formaldehyde (OR 8.61, 95% CI, 1.08, 68.8). However, again these associations were lost dropping the most symptomatic subject discussed above. Four-day moving averages were not significant but the ORs were elevated for acetone (OR 3.19, $p < 0.13$) and formaldehyde (OR 5.42, $p<0.16$).

Given the above results for lag models, results presented below will focus on lag 0 and 1 exposures.

4.5.3.3. Single pollutant models for asthma symptoms:
The two binary symptom score variables (as described above) were analyzed as dependent variables with GEE. The best working correlation was found to be AR1. Odds ratios and 95% confidence intervals (CI) for symptom models are expressed at mean air pollutant levels. Models were separately tested for confounding by: 1) temperature measured at the central sites; 2) respiratory tract infections; and 3) weekend. Regression parameters for air pollutants were not confounded by temperature or weekend. Respiratory infection reports were significantly associated with asthma symptom scores > 1, OR 3.40 (95% CI, 1.74, 6.64) and with scores > 2, OR 5.62 (95% CI, 1.97, 16.0). Respiratory infections positively confounded the air pollutants. For instance, the log odds for 1-hr NO_2 increased from 0.0420 to 0.0807 per ppb and the model deviance decreased by 103. An interaction term between the air pollutants and respiratory infections did not improve model fit. For instance, excluding the two subjects with invalid respiratory infection data and person-days with missing respiratory infection data, the log odds for 8-hr NO_2 increased from 0.1469 ± 0.0656 to 0.1706 ± 0.0716 per ppb, and the model deviance decreased by 10 after adding the respiratory infection variable to the model. A product term between the air pollutants and respiratory infections did not improve model fit. For most univariate pollutant models, regression parameters increased after excluding the two subjects with invalid respiratory infection data.

Table 4.27 shows results of the multivariate GEE models for the two binary symptom score variables in relation to mean concentrations of lag 0 and lag 1 criteria air pollutant gases and ambient VOCs, controlling for respiratory infections. Positive associations were found for criteria air pollutant gases, with stronger associations for lag 0 than for lag 1 exposures. Lag 0 ozone was significantly associated with more severe asthma symptoms interfering with daily activities (asthma symptom score > 2) but not bothersome or more severe symptoms (asthma symptom score > 1). The risk of symptom scores > 2 was over three times higher for an increase to the mean 1-hr ozone level of 25 ppb or 8-hr level of 17 ppb. The positive relationships between asthma symptoms and NO_2 were stronger for the 8-hr than the 1-hr averaging time, which was positive but nonsignificant. Both symptom variables were significantly associated with 8-hr NO_2. Asthma symptom scores > 1 were positively and significantly associated with both the 1-hr and 8-hr averaging times for SO_2. Asthma symptom scores > 2 were positively and significantly associated with 8-hr SO_2, although 1-hr SO_2 showed an OR of similar magnitude ($p = 0.18$). Asthma symptoms were not associated with CO.

Symptom scores > 1 were positively and significantly associated with lag 1 acetaldehyde and formaldehyde, but not lag 0 carbonyl compounds. Asthma symptoms scores > 2 were not significantly associated with acetaldehyde, but were positively associated with lag 0 and lag 1 acetone and lag 0 formaldehyde. The association with formaldehyde was strong (OR 7.30, $p < 0.05$).

Many models for the relationship between asthma symptom scores > 1 and the other non-carbonyl VOCs were positive and significant or near significant, including benzene, ethylbenzene, tetrachloroethylene, toluene, and *m,p*-xylene and *o*-xylene. Symptom scores > 1 were not associated with lag 0 1,3-butadiene, chloromethane, *p*-dichlorobenzene, methylene chloride or styrene, but there was some suggestion of an association with lag 1 1,3-butadiene ($p < 0.08$). None of the non-carbonyl VOCs were associated with asthma symptom scores > 2.

Table 4.27. Relationship of asthma symptoms in asthmatic children to increases in ambient VOCs and criteria air pollutant gases. Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Pollutant variable[a]	Air pollutant mean (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[c]	Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[d]
O_3 1-hr max, lag 0	25	1.06 (0.54, 2.08)	3.58 (1.12, 11.4)*
lag 1		1.04 (0.51, 2.12)	0.74 (0.34, 1.59)
O_3 8-hr max, lag 0	17	0.84 (0.43, 1.67)	3.11 (1.05, 9.24)*
lag 1		1.31 (0.68, 2.54)	1.09 (0.59, 2.01)
NO_2 1-hr max, lag 0	7	1.76 (0.88, 3.53)	2.30 (0.48, 11.1)
lag 1		2.00 (0.90, 4.46)	0.73 (0.10, 5.35)
NO_2 8-hr max, lag 0	6	2.79 (1.21, 6.43)*	4.21 (1.07, 16.5)*
lag 1		1.99 (0.72, 5.52)	1.20 (0.08, 18.4)
SO_2 1-hr max, lag 0	7	1.60 (1.18, 2.16)**	1.75 (0.78, 3.90)
lag 1		1.21 (0.85, 1.71)	0.62 (0.16, 2.37)
SO_2 8-hr max, lag 0	5	1.51 (1.13, 2.00)**	1.86 (1.18, 2.94)**
lag 1		1.24 (0.94, 1.63)	0.82 (0.26, 2.56)
CO 1-hr max, lag 0	8	0.93 (0.38, 2.31)	0.34 (0.02, 6.63)
lag 1		1.18 (0.65, 2.13)	1.45 (0.38, 5.52)

Table 4.27. (continued)

Pollutant variable[a]	Air pollutant mean (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[c]	Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[d]
CO 8-hr max, lag 0	5	0.92 (0.37, 2.25)	0.35 (0.02, 5.96)
lag 1		1.35 (0.64, 2.82)	1.81 (0.22, 14.6)
Acetaldehyde, lag 0	3.11	2.19 (0.60, 8.02)	2.90 (0.42, 19.9)
lag 1		2.51 (1.42, 4.42)**	2.09 (0.72, 6.05)
Acetone, lag 0	7.11	1.16 (0.64, 2.09)	2.70 (1.22, 5.97)*
lag 1		1.18 (0.74, 1.88)	2.23 (1.19, 4.20)*
Formaldehyde, lag 0	7.21	1.30 (0.33, 5.02)	7.30 (1.46, 36.4)*
lag 1		2.64 (1.12, 6.21)*	2.27 (0.43, 11.9)
Benzene, lag 0	1.82	1.44 (1.03, 2.02)*	0.58 (0.15, 2.15)
lag 1		1.11 (0.71, 1.73)	0.92 (0.43, 1.97)
1,3-Butadiene, lag 0	0.51	1.28 (0.85, 1.94)	0.63 (0.16, 2.46)
lag 1		1.59 (0.95, 2.65)	1.17 (0.39, 3.52)
Chloromethane, lag 0	0.58	1.48 (0.61, 3.54)	0.61 (0.18, 1.98)
lag 1		0.98 (0.24, 3.99)	0.44 (0.11, 1.82)
p_Dichlorobenzene, lag 0	0.15	1.19 (0.85, 1.67)	0.74 (0.30, 1.81)
lag 1		1.21 (0.86, 1.72)	1.04 (0.58, 1.85)
Ethylbenzene, lag 0	0.59	1.47 (1.10, 1.96)**	1.10 (0.48, 2.52)
lag 1		1.22 (0.88, 1.69)	1.17 (0.60, 2.26)
Methylene Chloride, lag 0	1.22	1.11 (0.88, 1.42)	0.73 (0.40, 1.33)
lag 1		0.95 (0.76, 1.19)	0.80 (0.63, 1.02)
Styrene, lag 0	0.10	1.15 (0.83, 1.58)	1.23 (0.71, 2.14)
lag 1		1.19 (0.84, 1.69)	1.44 (0.79, 2.60)

Table 4.27. (continued)

Pollutant variable[a]	Air pollutant mean (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[c]	Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[d]
Tetrachloroethylene, lag 0	0.51	1.48 (1.12, 1.95)**	0.88 (0.42, 1.86)
lag 1		1.16 (0.77, 1.76)	1.28 (0.58, 2.84)
Toluene, lag 0	7.17	1.53 (0.98, 2.38)	0.88 (0.25, 3.12)
lag 1		1.24 (0.81, 1.92)	0.83 (0.26, 2.64)
m,p-Xylene, lag 0	3.07	1.52 (1.01, 2.28)*	0.89 (0.22, 3.66)
lag 1		1.27 (0.85, 1.91)	1.09 (0.42, 2.85)
o-Xylene, lag 0	0.94	1.43 (1.00, 2.05)	0.89 (0.25, 3.19)
lag 1		1.26 (0.86, 1.84)	1.11 (0.48, 2.53)

[a] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant, controlling for respiratory infections (2 subjects with invalid respiratory infection data are excluded). Regression models involve data from 20 children over 74 days for SO_2, CO, and O_3 (887 person-days) 74 days for VOCs (938 person-days), 69 days for NO_2 (817 person-days) and 69 days for carbonyls (860 person-days). Pollutant concentrations are from the same day as symptom reports (lag 0).

[c] The asthma symptom severity score was dichotomized to: 1) no symptoms, symptoms not bothersome, versus 2) symptoms bothersome or more severe, including symptoms interfering with daily activities.

[d] The asthma symptom severity score was dichotomized to: 1) no symptoms or symptoms not interfering with daily activities, versus 2) symptoms interfering with daily activities.

* $p < 0.05$; ** $p < 0.01$.

One subject, who had the highest number of symptom reports, including symptom scores over 2, was influential in regression models for symptom scores > 2. This is was 13 year-old male who was among the most compliant subjects chosen for the personal exposure assessment project (ID 2497). He was not on anti-inflammatory medications and had the worst predicted FEV_1: pre-study 40%, post-study, 63%. Dropping this subject led to similar ORs for models involving symptom scores > 1, and actually increased ORs for models involving symptom scores > 0 (not shown in Table 4.26). However, in models for symptom scores > 2, ORs were in some cases halved or worse. The OR for lag 0 NO_2 was 1.37, for lag 0 acetone was 1.63, and for lag 0 formaldehyde 2.57, and none were significant.

4.5.3.4. Two-pollutant models for asthma symptoms:

The focus of the two-pollutant models is on exposures that were significant or nearly so in their respective single-pollutant models. Ambient carbonyl compounds (acetone and formaldehyde) were each regressed with 1-hr O_3, 8-hr NO_2 or 8-hr SO_2 in models testing for risk of asthma symptoms scores > 2. Lag 1 acetaldehyde and lag 1 formaldehyde were each regressed with lag 0 8-hr SO_2 or 8-hr NO_2 in models testing for risk of asthma symptoms scores > 1. Other VOCs (benzene, ethylbenzene, tetrachloroethylene, toluene, and *m,p*-xylene and *o*-xylene) were each regressed together with 8-hr SO_2 or 8-hr NO_2 in models testing for risk of asthma symptoms scores > 1. Interactions between criteria pollutant gases and ambient VOCs were tested first. There were no interactions between criteria pollutant gases and non-carbonyl VOCs. In relation to symptom scores > 2 there was a significant interaction between 1-hr O_3 and acetone (β 0.0086, SE 0.0028, $p < 0.002$) and between 8-hr NO_2 and acetone (β 0.0530, SE 0.0155, $p < 0.0007$). In relation to symptom scores > 2 the interaction term was nearly significant between 1-hr O_3 and formaldehyde (β 0.0105, SE 0.0056, p=0.06) and was significant between 8-hr NO_2 and formaldehyde (β 0.0997, SE 0.0263, $p < 0.0002$) and between 8-hr SO_2 and formaldehyde (β 0.0858, SE 0.0429, p<0.05). Regression models were then tested to assess whether criteria pollutant gases confounded associations of symptoms with ambient VOCs (Table 4.28). We present 2-pollutant models for carbonyls with criteria pollutant gases, but note that the presence of significant interactions makes the presence of confounding less important.

Table 4.28 shows that odds ratios for symptoms > 2 and acetone in two-pollutant models with O_3 and NO_2 were unchanged from the model with acetone alone, and minimally reduced (15%) in the regression model with SO_2. In the same models, odds ratios for O_3 and NO_2 were reduced by 21% and 53%, respectively, and the OR for SO_2 was reduced by 23%. Regression models for symptoms > 2 and formaldehyde regressed with O_3, NO_2 or SO_2 showed that regression parameters and standard errors were unstable for nearly all independent variables, suggesting multicollinearity. The presence of interaction supports this view and argues against any clear interpretation of confounding. In the model with formaldehyde and O_3, the association with O_3 was reduced by 20% whereas the association with formaldehyde reduced by 60% and the 95% confidence interval was wide. On the other hand, the model with formaldehyde and NO_2, the association with NO_2 was reduced by 64% whereas the association with formaldehyde reduced by only 3%, however, the 95% confidence intervals were wide for both pollutants. In the model with formaldehyde and SO_2, the association with SO_2 was still significant and was minimally changed in contrast to formaldehyde.

For symptoms > 1 and the other VOCs regressed with NO_2 or SO_2 in Table 4.28, regression parameters for VOCs were, in general, reduced more than the co-regressed criteria pollutant gas. This was most clearly shown in models for benzene, toluene and xylene compounds, primarily when regressed with SO_2. However, for NO_2 plus VOC models, ORs were reduced and confidence intervals widened for both pollutants compared with single pollutant models. Regression parameters for lag 1 formaldehyde and acetaldehyde were somewhat more stable than for NO_2. There was evidence for multicollinearity in most models. For instance, in the models for ethylbenzene, ORs were reduced and confidence intervals widened for all pollutants compared with single pollutant models that showed significant associations for both pollutants. This is not surprising given that the pollutants were moderately correlated with each other (Table 4.26). Therefore, although there was limited evidence that criteria pollutant gases confounded associations with non-carbonyl VOCs, this view is clouded by multicollinearity in the regression models.

Table 4.28. Two-pollutant models for the relationship of asthma symptoms in children to concentrations of ambient VOCs controlling for criteria pollutant gases; Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Independent variable[a]	Mean concentration (ppb)	Odds ratios (95% CI)[b] for asthma symptoms that interfered with daily activities per increase to mean concentration of pollutant[c]	
Carbonyl Compounds		Single pollutant	Two-pollutant
Model 1:			
Acetone	7.11	2.70 (1.22, 5.97)*	2.77 (0.96, 7.98)
1-hr max O_3	25	3.58 (1.12, 11.4)*	2.82 (0.99, 8.02)
Model 2:			
Acetone	7.11	2.70 (1.22, 5.97)*	2.71 (1.10, 6.68)*
8-hr max NO_2	6	4.21 (1.07, 16.5)*	1.98 (0.82, 4.71)
Model 3:			
Acetone	7.11	2.70 (1.22, 5.97)*	2.29 (1.08, 4.86)*
8-hr max SO_2	5	1.86 (1.18, 2.94)**	1.43 (0.99, 2.06)
Model 4:			
Formaldehyde	7.21	7.30 (1.46, 36.4)*	2.92 (0.28, 30.5)
1-hr max O_3	25	3.58 (1.12, 11.4)*	2.85 (0.81, 10.0)
Model 5:			
Formaldehyde	7.21	7.30 (1.46, 36.4)*	7.08 (0.11, 466)
8-hr max NO_2	6	4.21 (1.07, 16.5)*	1.50 (0.36, 6.32)
Model 6:			
Formaldehyde	7.21	7.30 (1.46, 36.4)*	2.86 (0.39, 20.8)
8-hr max SO_2	5	1.86 (1.18, 2.94)**	1.55 (1.08, 2.23)*
Model 7:			
Benzene	1.82	1.47 (1.06, 2.03)*	1.13 (0.72, 1.78)
8-hr max NO_2	6	2.81 (1.26, 6.25)*	2.46 (0.89, 6.79)
Model 8:			
Benzene	1.82	1.43 (1.04, 1.98)*	1.06 (0.71, 1.59)
8-hr max SO_2	5	1.52 (1.15, 2.01)**	1.49 (1.05, 2.10)*

Table 4.28. (continued)

Independent variable[a]	Mean concentration (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[d]	
Other VOCs		Single pollutant	Two-pollutant
Model 9:			
Ethylbenzene	0.59	1.47 (1.08, 2.01)**	1.26 (0.80, 1.98)
8-hr max NO_2	6	2.81 (1.26, 6.25)*	1.83 (0.55, 6.13)
Model 10:			
Ethylbenzene	0.59	1.50 (1.11, 2.03)**	1.20 (0.74, 1.95)
8-hr max SO_2	5	1.52 (1.15, 2.01)**	1.35 (0.84, 2.17)
Model 11:			
Tetrachloroethylene	0.51	1.49 (1.09, 2.04)*	1.24 (0.84, 1.81)
8-hr max NO_2	6	2.81 (1.26, 6.25)*	2.13 (0.80, 5.69)
Model 12:			
Tetrachloroethylene	0.51	1.50 (1.11, 2.04)**	1.20 (0.77, 1.86)
8-hr max SO_2	5	1.52 (1.15, 2.01)**	1.40 (0.95, 2.08)
Model 13:			
Toluene	7.17	1.58 (0.99, 2.54)	1.26 (0.69, 2.29)
8-hr max NO_2	6	2.81 (1.26, 6.25)*	2.09 (0.72, 6.04)
Model 14:			
Toluene	7.17	1.55 (0.95, 2.53)	1.15 (0.61, 2.15)
8-hr max SO_2	5	1.52 (1.15, 2.01)**	1.44 (0.97, 2.13)
Model 15:			
m,p-Xylene	3.07	1.56 (1.01, 2.41)*	1.25 (0.75, 2.09)
8-hr max NO_2	6	2.81 (1.26, 6.25)*	2.04 (0.75, 5.53)
Model 16:			
m,p-Xylene	3.07	1.55 (1.01, 2.40)*	1.16 (0.68, 1.98)
8-hr max SO_2	5	1.52 (1.15, 2.01)**	1.42 (0.97, 2.08)

Table 4.28. (continued)

Independent variable[a]	Mean concentration (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant[d]	
Other VOCs		Single pollutant	Two-pollutant
Model 17:			
o-Xylene	0.94	1.44 (0.98, 2.10)	1.08 (0.71, 1.64)
8-hr max NO_2	6	2.81 (1.26, 6.25)*	2.49 (0.98, 6.30)
Model 18:			
o-Xylene	0.94	1.44 (0.99, 2.12)	1.04 (0.66, 1.64)
8-hr max SO_2	5	1.52 (1.15, 2.01)**	1.49 (1.04, 2.14)*
Model 19:			
Acetaldehyde, lag 1	3.11	2.53 (1.20, 5.33)*	2.03 (1.01, 4.08)*
8-hr max NO_2	6	2.78 (1.27, 6.08)*	1.58 (0.76, 3.26)
Model 20:			
Acetaldehyde, lag 1	3.11	2.55 (1.32, 4.93)**	1.71 (1.00, 2.92)*
8-hr max SO_2	5	1.52 (1.16, 1.99)**	1.34 (1.02, 1.75)*
Model 21:			
Formaldehyde, lag 1	7.21	4.15 (1.48, 11.6)**	2.98 (1.08, 8.25)*
8-hr max NO_2	6	2.78 (1.27, 6.08)*	1.54 (0.72, 3.31)
Model 22:			
Formaldehyde, lag 1	7.21	2.75 (1.20, 6.29)*	1.61 (0.63, 4.08)
8-hr max SO_2	5	1.52 (1.16, 1.99)**	1.40 (1.03, 1.90)*

[a] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant, controlling for respiratory infections (2 subjects with invalid respiratory infection data are excluded).

[c] The asthma symptom severity score was dichotomized to: 1) no symptoms or symptoms not interfering with daily activities, versus 2) symptoms interfering with daily activities.

[d] The asthma symptom severity score was dichotomized to: 1) no symptoms, symptoms not bothersome, versus 2) symptoms bothersome or more severe, including symptoms interfering with daily activities.

- $p < 0.05$; ** $p < 0.01$.

4.5.3.5. Particulate Air Pollutants:

Table 4.29 shows results of multivariate GEE models for bothersome or more severe asthma symptoms in relation to concentrations of ambient gravimetric PM_{10}, EC, and OC, and TEOM PM_{10}. Because particle mass was measured for only a subset of days, the more severe symptom variable was not examined because of the limitation in the number of gravimetric observations on days when subjects reported symptom scores > 2 (9 out of 408 person-days) as compared with a scores > 1 (27 out of 408 person-days). The asthma symptom score was > 1 on 6 out 54 person-days for TEOM data. Also shown in Table 4.29 are two-pollutant models for gravimetric PM_{10} and either EC or OC to test whether associations with EC or OC are confounded by PM_{10} and whether associations with PM_{10} are confounded by EC. Gravimetric variables were positively associated with symptoms with strengths of association being OC > EC > PM_{10}. In two-pollutant models, the associations with EC and OC were not confounded by PM_{10}, but the OR for PM_{10} was reduced from 1.83 to 1.04 when regressed with EC. Regressing OC with PM_{10} also reduced the OR for PM_{10} to 0.99 (not shown in Table). Confidence limits widened for all pollutants due to variance inflation (recall pollutant correlations were R > 0.8). Despite the small number of observations, TEOM PM_{10} was significantly associated with asthma symptoms. Strengths of association for the various TEOM averaging times showed the relative magnitudes to be: 1-hr ≅ 8-hr > 24-hr PM_{10}.

4.5.4. Regression Analysis of Peak Expiratory Flow and Ambient Air Pollutants:

For multiple regression analyses of PEF we employed the general linear mixed model as described above. PEF maneuvers with reproducibility > 10% were excluded. Inclusion of these PEF observations made little difference in results though. Regression models were examined separately for morning and evening PEF. Evening PEF was examined in relation to lag 0 air pollutant concentrations, and morning PEF was examined in relation to lag 1 air pollutant concentrations. Models were separately tested for confounding by: 1) temperature measured at the central sites; 2) respiratory tract infections; and 3) weekend. An autoregressive parameter was needed to adjust for autocorrelated error terms. Respiratory infections were associated with significant deficits in morning PEF of –9.01 L/min and borderline significant deficits (p < 0.09) in evening deficits of –8.04 L/min. Inclusion of respiratory infections led to a small amount of confounding of air pollutant parameters and improved model fit (AIC decreased over 200 in all models).

Table 4.29. Relationship of asthma symptoms[a] in asthmatic children to particulate air pollutants and elemental and organic carbon fractions. Nov 4 through Dec 28, 1999, Huntington Park region, Los Angeles County, California.

Pollutant variable[a]	Mean air pollutant ($\mu g/m^3$)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms[c] per increase to mean concentration of pollutant	
Nov 4 – 26, Dec 8 and 14 1999:		Single Pollutant	2-Pollutant[d]
Gravimetric PM_{10} 24-hr mean	60	1.83 (1.18, 2.84)**	with Elemental Carbon: 1.04 (0.36, 2.99)
			with Organic Carbon: 0.99 (0.30, 3.20)
Elemental Carbon 24-hr mean	5.09	2.95 (1.21, 7.18)*	with PM_{10}: 2.88 (0.73, 11.3)
Organic Carbon 24-hr mean	9.47	3.62 (1.25, 10.5)*	with PM_{10}: 3.65 (0.66, 20.2)
Dec 19 – 28, 1999:			
TEOM PM_{10} 1-hr max	92	20.4 (1.26, 331)*	--
TEOM PM_{10} 8-hr max	64	19.9 (1.46, 271)*	--
TEOM PM_{10} 24-hr mean	52	8.95 (1.00, 80.2)*	--

[a] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant. Elemental and Organic Carbon models control for respiratory infections (2 subjects with invalid respiratory infection data are excluded). Regression models involve data from 20 children over 10 days (54 person-days) for TEOM PM_{10}, and 24 days (351 person-days) for gravimetric PM_{10}, elemental and organic carbon. Pollutant concentrations are from the same day as symptom reports (lag 0).

[c] the asthma symptom severity score was dichotomized to: 1) no symptoms, symptoms not bothersome, versus 2) symptoms bothersome or more severe, including interference with daily activities.

[d] Gravimetric PM_{10} was regressed with Elemental Carbon. Elemental and Organic Carbon was regressed with Gravimetric PM_{10}.

* $p < 0.05$; ** $p < 0.01$.

Table 4.30 shows results of multivariate models for morning PEF versus lag 1 ambient VOCs, and evening PEF versus lag 0 air pollutants, controlling for respiratory infections. Associations are given at the mean concentration. Table 4.31 shows PEF modeled on criteria air pollutant gases in the same manner. None of the pollutant models show any significant deficit in PEF in relation to air pollution. The model for morning PEF versus formaldehyde actually shows a significant increase in PEF (Table 4.30). This is unlikely to be causal and is not surprising given that 40 models were tested and at the 5% alpha level, 2 models are expected to be significant. Model fit was marginally improved by temperature and weekend, and null associations with pollutants were not altered.

Table 4.32 shows results of multivariate models for morning PEF versus lag 1 ambient particulate air pollutants, and evening PEF versus lag 0 ambient particulate air pollutants, controlling for respiratory infections. TEOM PM_{10} was associated with significant PEF deficits in the morning, with particularly large deficits for 1-hr PM_{10} of –64.5 L/min at a mean of 92 $\mu g/m^3$. However, there were no consistent deficits in evening PEF in relation to TEOM PM_{10}. Gravimetric PM_{10}, EC and OC showed inverse relationships with evening PEF but none were significant and there was no suggestion of an association with morning PEF.

Lag pollutant models did not show any association of PEF deficits with any ambient pollutant measure on 1 to 2 days in the past.

Table 4.30. The relationship of daily peak expiratory flow rates in asthmatic children to ambient concentrations of volatile organic compounds; Nov 4, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Dependent Variable[a]	Independent Variable[b]	No. Obs.	Mean Concentration (ppb)	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 Acetaldehyde	745	3.11	0.73 (-8.13, 9.59)
PM PEF	Lag 0 Acetaldehyde	771		1.70 (-7.67, 11.1)
AM PEF	Lag 1 Acetone	745	7.11	4.54 (-0.56, 9.64)
PM PEF	Lag 0 Acetone	771		3.61 (-2.20, 9.42)
AM PEF	Lag 1 Formaldehyde	745	7.21	11.4 (0.25, 22.5)*
PM PEF	Lag 0 Formaldehyde	771		7.55 (-4.51, 19.6)
AM PEF	Lag 1 Benzene	812	1.82	-1.22 (-6.12, 3.67)
PM PEF	Lag 0 Benzene	834		-3.47 (-9.03, 2.10)
AM PEF	Lag 1 1,3-Butadiene	812	0.51	0.76 (-4.01, 5.54)
PM PEF	Lag 0 1,3-Butadiene	834		-2.24 (-7.44, 2.96)
AM PEF	Lag 1 Chloromethane	798	0.58	5.57 (-4.93, 16.1)
PM PEF	Lag 0 Chloromethane	820		-1.10 (-12.4, 10.2)

Table 4.30. (continued)

Dependent Variable[a]	Independent Variable[b]	No. Obs.	Mean Concentration (ppb)	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 p-Dichlorobenzene	812	0.15	0.82 (-3.13, 4.78)
PM PEF	Lag 0 p-Dichlorobenzene	834		-0.75 (-5.15, 3.65)
AM PEF	Lag 1 Ethylbenzene	812	0.59	0.59 (-3.28, 4.46)
PM PEF	Lag 0 Ethylbenzene	834		0.38 (-3.90, 4.65)
AM PEF	Lag 1 Methylene Chloride	812	1.22	1.91 (-1.33, 5.15)
PM PEF	Lag 0 Methylene Chloride	834		-1.06 (-4.75, 2.63)
AM PEF	Lag 1 Styrene	812	0.10	0.79 (-2.56, 4.13)
PM PEF	Lag 0 Styrene	834		2.56 (-1.24, 6.35)
AM PEF	Lag 1 Tetrachloroethylene	812	0.51	3.90 (-0.65, 8.45)
PM PEF	Lag 0 Tetrachloroethylene	834		-0.66 (-5.60, 4.29)
AM PEF	Lag 1 Toluene	812	7.17	0.53 (-4.49, 5.55)
PM PEF	Lag 0 Toluene	834		-1.28 (-6.82, 4.25)
AM PEF	Lag 1 m,p-Xylene	812	3.07	0.21 (-4.50, 4.93)
PM PEF	Lag 0 m,p-Xylene	834		-1.14 (-6.32, 4.03)
AM PEF	Lag 1 o-Xylene	812	0.94	0.03 (-4.56, 4.62)
PM PEF	Lag 0 o-Xylene	834		-0.01 (-5.07, 5.05)

[a] Morning peak expiratory flow rate (AM PEF) and evening peak expiratory flow rate (PM PEF).

[b] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites. Pollutant concentrations are from the day previous to the morning PEF (lag 1) and from the same day (lag 0) as evening PEF.

[c] PEF change and 95% confidence intervals (CI) are from mixed linear regression models adjusting for respiratory infections, and estimate the lung function response for an mean change in air pollutant concentration.

* $p < 0.05$; ** $p < 0.01$.

Table 4.31. The relationship of daily peak expiratory flow rates in asthmatic children to concentrations of ambient criteria pollutant gases; Nov 11, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Dependent Variable[a]	Independent Variable[b]	No. Obs.	Mean Concentration (ppb)	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 O_3 1-hr max	757	25	-5.12 (-11.9, 1.71)
PM PEF	Lag 0 O_3 1-hr max	787		6.16 (-1.77, 14.1)
AM PEF	Lag 1 O_3 8-hr max	757	17	-3.75 (-10.0, 2.52)
PM PEF	Lag 0 O_3 8-hr max	787		4.37 (-2.94, 11.7)
AM PEF	Lag 1 NO_2 1-hr max	685	7	5.22 (-3.52, 14.0)
PM PEF	Lag 0 NO_2 1-hr max	715		3.53 (-6.56, 13.6)
AM PEF	Lag 1 NO_2 8-hr max	685	6	7.18 (-2.67, 17.0)
PM PEF	Lag 0 NO_2 8-hr max	715		6.33 (-4.87, 17.5)
AM PEF	Lag 1 SO_2 1-hr max	757	7	0.52 (-3.84, 4.87)
PM PEF	Lag 0 SO_2 1-hr max	787		-0.80 (-5.67, 4.07)
AM PEF	Lag 1 SO_2 8-hr max	757	5	0.32 (-3.86, 4.51)
PM PEF	Lag 0 SO_2 8-hr max	787		0.69 (-3.94, 5.31)
AM PEF	Lag 1 CO 1-hr max	757	8	-0.36 (-6.41, 5.70)
PM PEF	Lag 0 CO 1-hr max	787		-0.91 (-7.92, 6.09)
AM PEF	Lag 1 CO 8-hr max	757	5	0.08 (-6.98, 7.15)
PM PEF	Lag 0 CO 8-hr max	787		-1.66 (-9.65, 6.34)

[a] Morning peak expiratory flow rate (AM PEF) and evening peak expiratory flow rate (PM PEF).

[b] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites. Pollutant concentrations are from the day previous to the morning PEF (lag 1) and from the same day (lag 0) as evening PEF.

[c] PEF Change and 95% Confidence Intervals (CI) are from mixed linear regression models adjusting for respiratory infections, and estimate the lung function response for an mean change in air pollutant concentration.

* $p < 0.05$; ** $p < 0.01$.

Table 4.32. The relationship of daily peak expiratory flow rates in asthmatic children to particulate air pollutants and elemental and organic carbon fractions. Nov 11, 1999 through Jan 23, 2000, Huntington Park region, Los Angeles County, California.

Dependent Variable[a]	Independent Variable[b]	No. Obs.	Mean Concentration (ppb)	PEF Change (95% CI)[c] per Mean increase in VOC
AM PEF	Lag 1 TEOM PM_{10} 1-hr max	26	92	-64.5 (-121, -7.94)*
PM PEF	Lag 0 TEOM PM_{10} 1-hr max	42		14.0 (-54.8, 82.8)
AM PEF	Lag 1 TEOM PM_{10} 8-hr max	26	64	-25.1 (-52.3, 2.12)
PM PEF	Lag 0 TEOM PM_{10} 8-hr max	42		30.5 (-19.8, 80.8)
AM PEF	Lag 1 TEOM PM_{10} 24-hr mean	26	52	-20.2 (-35.4, -4.92)*
PM PEF	Lag 0 TEOM PM_{10} 24-hr mean	42		18.8 (-28.2, 65.8)
AM PEF	Lag 1 Gravimetric PM_{10} 24-hr mean	315	60	0.52 (-9.51, 10.5)
PM PEF	Lag 0 Gravimetric PM_{10} 24-hr mean	332		-5.95 (-16.6, 4.71)
AM PEF	Lag 1 Elemental Carbon 24-hr mean	315	5.09	-1.4 (-12.4, 9.59)
PM PEF	Lag 0 Elemental Carbon 24-hr mean	332		-7.79 (-18.5, 2.94)
AM PEF	Lag 1 Organic Carbon 24-hr mean	315	9.47	0.59 (-11.8, 13.0)
PM PEF	Lag 0 Organic Carbon 24-hr mean	332		-9.83 (-22.3, 2.68)

[a] Morning peak expiratory flow rate (AM PEF) and evening peak expiratory flow rate (PM PEF).

[b] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites. Pollutant concentrations are from the day previous to the morning PEF (lag 1) and from the same day (lag 0) as evening PEF.

[c] PEF Change and 95% Confidence Intervals (CI) are from mixed linear regression models adjusting for respiratory infections (2 subjects with invalid respiratory infection data are excluded), and estimate the lung function response for an mean change in air pollutant concentration. Regression models involve data from 20 children over 10 days for TEOM PM_{10} (Dec 19 – 28, 1999) and over 24 days for gravimetric PM_{10}, elemental and organic carbon (Nov 4 – 26, Dec 8 and 14 1999).

* $p < 0.05$; ** $p < 0.01$.

4.5.5. Regression Analysis Testing for Interaction of Ambient Air Pollutants with Asthma Severity Level and with Anti-inflammatory Medications Use:

Models for symptom scores > 1 were tested with interaction terms between ambient air pollutants and asthma severity level or anti-inflammatory medications use, controlling for respiratory infections (described above in Section 4.5.1.). There were no significant interactions between any of the ambient air pollutants and classification of asthma severity. All *p*-values for these interaction terms were ≥ 0.2. In general, regression parameters were either moderately greater or close in magnitude for more severely asthmatic subjects (N = 6) as compared with less severely asthmatic subjects (N = 14). Parameters were generally positive for both groups. Relative strengths of association appeared different between severity groups for O_3, acetaldehyde and toluene, although regression slopes were not significantly different. For O_3, there was a positive association in the more severe asthmatics (OR 1.71, 95% CI, 1.33, 2.20) versus a nonsignificant negative parameter in the less severe asthmatics (OR 0.27, 95% CI, 0.02, 4.59). For acetaldehyde, there was a smaller positive relationship in the more severe asthmatics (OR 1.76, 95% CI, 0.32, 9.67) versus the less severe asthmatics (OR 5.10, 95% CI, 1.23, 21.1). Recall that for the group as a whole, acetaldehyde was not significantly associated with symptoms. For toluene, there was a smaller positive relationship in the more severe asthmatics (OR 1.27, 95% CI, 0.78, 2.07) versus the less severe asthmatics (OR 2.49, 95% CI, 1.12, 5.52).

Interactions between the ambient air pollutants and regular use of anti-inflammatory medications were not significant in most models (p ≥ 0.10) with the exception of 8-hr CO and acetaldehyde ($p < 0.05$) and formaldehyde ($p < 0.07$) (Table 4.33), which revealed higher symptom response magnitudes among those not on anti-inflammatory medications as compared with those on anti-inflammatory medications (Table 7). The regression parameter was also larger for 1,3-butadiene for those not on anti-inflammatory medications, but not significantly different from those on the medications. In contrast, for 8-hr O_3 there was a higher response magnitude among those on anti-inflammatory medication as compared with those not on anti-inflammatory medications ($p < 0.07$). For the remaining models, although there were no significant differences between medication groups, those on anti-inflammatory medications generally showed regression parameters that were either slightly greater or close in magnitude to those not on anti-inflammatory medications. The product term models were robust to exclusion of individual subjects.

Table 4.33. Effect modification by anti-inflammatory medication use on the relationship of asthma symptoms[a] in children to increases in lag 0 ambient VOCs and criteria air pollutant gases.

Pollutant variable[a]	Mean air pollutant level (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant		
		Subjects on anti-inflammatory medications[c]	Subjects not on anti-inflammatory medications[d]	p-value for between-group product term
O_3 8-hr max	17	5.21 (0.89, 30.6)	0.30 (0.06, 1.57)	0.07
NO_2 8-hr max	6	2.00 (0.41, 9.68)	2.24 (0.56, 8.86)	0.39
SO_2 8-hr max	5	1.43 (0.81, 2.52)	1.32 (0.78, 2.22)	0.22
CO 8-hr max	5	0.19 (0.06, 0.66)	2.48 (1.21, 5.05)	0.008

Table 4.33 (continued)

Pollutant variable[a]	Mean air pollutant level (ppb)	Odds ratios (95% CI)[b] for bothersome or more severe asthma symptoms per increase to mean concentration of pollutant		
		Subjects on anti-inflammatory medications[c]	Subjects not on anti-inflammatory medications[d]	p-value for between-group product term
Acetaldehyde	3.11	0.16 (0.03, 0.84)	6.08 (2.31, 16.0)	0.03
Acetone	7.11	1.16 (0.31, 4.36)	1.11 (0.32, 3.92)	0.82
Formaldehyde	7.21	0.17 (0.03, 1.11)	3.58 (0.86, 14.8)	0.07
Benzene	1.82	1.43 (0.70, 2.94)	1.21 (0.71, 2.07)	0.33
1,3-Butadiene	0.51	0.62 (0.32, 1.22)	1.66 (1.04, 2.65)	0.17
Chloromethane	0.58	0.96 (0.16, 5.58)	1.54 (0.76, 3.14)	0.96
p_Dichlorobenzene	0.15	0.83 (0.47, 1.47)	1.32 (0.88, 1.99)	0.52
Ethylbenzene	0.59	1.00 (0.57, 1.76)	1.49 (1.03, 2.16)	0.99
Methylene Chloride	1.22	0.81 (0.52, 1.26)	1.23 (0.86, 1.76)	0.35
Styrene	0.10	1.14 (0.60, 2.14)	1.08 (0.70, 1.66)	0.69
Tetrachloroethylene	0.51	1.01 (0.57, 1.77)	1.48 (0.95, 2.31)	0.98
Toluene	7.17	0.72 (0.32, 1.60)	1.82 (1.02, 3.26)	0.42
m,p-Xylene	3.07	0.89 (0.41, 1.93)	1.64 (0.94, 2.88)	0.77
o-Xylene	0.94	0.99 (0.49, 2.00)	1.46 (0.90, 2.360	0.98

[a] Air pollution measurements were made by the South Coast Air Quality Management District at the stationary outdoor monitoring sites.

[b] Odds Ratios and 95% confidence intervals (CI) are from generalized estimating equations, and estimate the relative risk of a symptom response for a mean change in the air pollutant, controlling for respiratory infections (2 subjects with invalid respiratory infection data are excluded).

[c] 6 subjects on inhaled corticosteroids, cromolyn or nedocromil, with a total of 343 person-days days for SO_2, CO, and O_3, 320 person-days for NO_2, 349 person-days for VOCs and 323 person-days for carbonyls.

[d] 14 subjects with a total of 544 person-days days for SO_2, CO, and O_3, 497 person-days for NO_2, 589 person-days for VOCs and 537 person-days for carbonyls.