CHARACTERIZING AND PREDICTING ULTRAFINE PARTICLE COUNTS IN CANADIAN HOMES, SCHOOLS, AND TRANSPORTATION ENVIRONMENTS: AN EXPOSURE MODELING STUDY WITH IMPLICATIONS IN ENVIRONMENTAL EPIDEMIOLOGY

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SHORT TITLE PROPOSED

Characterizing and predicting ultrafine particle counts in homes, schools, and transportation environments.

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ABSTRACT

Airborne particulate matter has a negative effect on respiratory health in both children and adults, and the ultrafine fraction of particulate air pollution is of particular interest owing to its increased ability to cause oxidative stress and inflammation in the lungs. In this investigation, our objective was to characterize ultrafine particle (UFP) counts in homes, schools, and transportation environments and to develop models to predict such exposures. A number of important determinants of UFP exposures were identified including ambient temperature and wind speed for transportation environments, outdoor UFPs for classrooms, and electric oven use, cigarette smoking, indoor relative humidity, and volume for homes. In general, our findings suggest that classrooms and transportation environments may be more suitable for UFP exposure modeling than homes. However, large diesel vehicles and in-school UFP sources had a negative influence on model performance, and future studies should include factors such as traffic counts/characteristics, vehicle ventilation settings, and in-school UFP sources to improve the predictive performance of the models presented. Nevertheless, our findings are encouraging in that we demonstrate for the first time the possibility of obtaining UFP exposure estimates for homes, schools, and transportation environments using models based on ambient weather data and other readily available determinant information. As such, similar models may be useful in population-based studies interested in the potential health effects of UFP exposures.

RESUME

La matière particulaire aéroportée a un effet négatif sur le système respiratoire des enfants et sur celui des adultes et la pollution de l'air engendrée par les particules ultra fines (PUF) demeure une source de préoccupation si on tient compte de leur possibilité de susciter le stress oxydatif lequel est précurseur de l'inflammation dans les poumons. L'objectif de la présente étude était de caractériser l'exposition aux PUF dans les maisons, les écoles, et l'environnement de systèmes de transport et de développer des modèles pour prédire ces expositions. Un nombre notable de déterminants liés à l'exposition aux PUF a été identifié dont la température ambiante et la vitesse du vent dans le cas l'environnement des transports, les PUF à la périphérie des écoles pour ce qui est des classes, et l'utilisation d'un four électrique, la fumée de cigarette, l'humidité relative et leur volume en ce qui a trait aux maisons. En général, l'investigation permet de suggérer que la modélisation de la concentration des PUF dans les classes des écoles et l'environnement de systèmes de transport est plus facile à réaliser que dans les maisons. Cependant, les véhicules fonctionnant au diésel et les sources internes de PUF dans les écoles ont un effet négatif sur la performance de notre modèle et les études futures devaient inclure l'évaluation de facteurs tels que le dénombrement et les caractéristiques des véhicules, l'aménagement de la ventilation dans les véhicules et les sources de PUF dans les écoles afin d'améliorer sa performance de prédiction. Néanmoins, notre exploration dans ce domaine est encourageante parce qu'elle montre pour une première fois la possibilité d'estimer l'exposition aux PUF dans les maisons, les écoles, et l'environnement des systèmes de transport en utilisant des modèles qui sont basés sur la cueillette simple de données telle la température ambiante ou encore ils sont basés sur de

l'information relativement facile à colliger. Ainsi, des modèles similaires peuvent être utilisés lors d'études appliquées sur les populations dont l'intérêt est la mesure des effets potentiels sur la santé de l'exposition aux PUF.

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DEDICATION

To my parents, Brenda and Wade Weichenthal.

CONTRIBUTIONS OF THE CO-AUTHORS

Scott Weichenthal (SW) wrote this thesis and was the principal author of all five manuscripts (Manuscripts A-D in the thesis and Manuscript E in the Appendix). **Dr. Claire Infante-Rivard (CIR)** was the principal investigator on the AllerGen grant and was **SW's** supervisor along with **Dr. André Dufresne (AD)**. **CIR** and **AD** participated in manuscript development and publication for all five manuscripts, and **AD** provided the French translation of the abstract presented in this thesis. **SW, CIR,** and **AD** collectively designed the home UFP exposure study (Manuscript B) and all participant homes were identified by **SW** and **AD.** The school (Manuscript D) and transportation environment (Manuscript C) studies were organized, planned, and conducted by **SW** under the guidance of **CIR** and **AD**. **SW** performed all of the statistical analysis under the guidance of **Dr. Lawrence Joseph**, who also assisted in writing the "statistical analysis" portion of three manuscripts.

ORIGINALITY STATEMENT

Ours is the only investigation to compare UFP levels in homes according to the type of home heating system. Likewise, we are the first to explore determinants of UFP exposures in classrooms during the winter months and the first to model such exposures. While several studies have examined UFP exposures in transportation environments, we are the first to model such exposures based on readily available ambient weather data and the first to test such models. Collectively, our study of UFP exposures in homes, schools, and transportation environments represents a meaningful contribution to the current body of knowledge regarding determinants of UFP exposures in these locations. In addition, our findings provide insight into the applicability and effectiveness of UFP exposure assessment models in large population-based studies interested in the health effects of UFP exposures.

LIST OF ACRONYMS AND ABBREVIATIONS

95% CI	95% confidence interval
^{o}C	Degree Celsius
%	Percent
>	Greater than
<	Less than
α	Alpha
Ach	Air exchange rate
ASHRAE	American Society of Heating and Refrigerating and Air-conditioning Engineers
β	Beta
BMA	Bayesian model averaging
cm	Centimeter
CPC	Condensation particle counter
CO_2	Carbon dioxide
DMA	Differential mobility analyzer
DNA	Deoxyribonucleic acid
h	Hour
H_m	Mixing height
IgE	Immunoglobin E
IL-13	Interleukin-13
K	Kelvin
km	Kilometer

LUR	Land use regression
OR	Odds ratio
mRNA	Messenger ribonucleic acid
nm	Nanometer
m	Meter
P	Pasquill stability class
PM	Particulate matter
$PM_{2.5}$	Particulate matter with an aerodynamic diameter less than 2.5 um
PM_4	Particulate matter with an aerodynamic diameter less than 4 um
PM_{10}	Particulate matter with an aerodynamic diameter less than 10 um
p.p.m	Parts per million
RH	Relative humidity
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
s	Second
SD	Standard deviation
SMPS	Scanning mobility particle sizer
Th1	T-helper type 1 lymphocytes
Th2	T-helper type 2 lymphocytes
UFP(s)	Ultrafine particle(s)
μm	Micrometer
U_z	Wind speed
VOC(s)	Volatile organic compound(s)

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1. INTRODUCTION

Genetic make-up and environment each play a crucial role in determining the onset of childhood asthma (Kleeberger and Peden, 2005; London, 2007; Yang et al., 2007). Indoor environmental risk factors are particularly important owing to the large amount of time children spend indoors. Indeed, several indoor environmental risk factors have been identified for childhood asthma including biological contaminants such as dust mite, cockroach, and cat allergens (Gold, 2000; Liu, 2004). However, evidence in support of previously suspected indoor chemical pollutants such as volatile organic compounds (VOCs) and nitrogen dioxide, while not to be discarded, remains inconsistent (Weichenthal et al., 2007c) (Appendix 1). As such, the identification of new indoor risk factors that initiate, intensify, or otherwise influence childhood asthma symptoms is essential if we hope to lessen the negative social and economic impact of this disease (Busse and Lemanske, 2001).

Recently, increasing interest has focused on ultrafine particles (UFPs) as a potential risk factor for childhood asthma because experimental studies in animals have consistently demonstrated their ability to cause oxidative stress and inflammation in the lungs (Oberdörster et al., 1994; Li et al., 1996; Afaq et al., 1998; Zheng et al., 1998; Brown et al., 2001; Dick et al., 2003; Zhou et al., 2003a; Zhou et al., 2003b; Gilmour MI et al., 2004; Gilmour PS et al., 2004; Shwe et al., 2005). However, exposure assessment is often difficult for UFPs in population-based studies owing to logistical and financial constraints which prevent the collection of detailed exposure information for large numbers of study participants (Sioutas et al., 2005). This challenge has been discussed previously (Needham and Sexton, 2000; Bradman and Whyatt, 2005; Özkaynak et al. 2005; Needham et al., 2005), and a combination of strategies may be necessary to obtain an accurate depiction of UFP exposures in epidemiological studies (Adgate

et al., 2000; Gilliland et al., 2005). In addressing this issue, one option is to collect detailed exposure information from a sub-set of participants and then use these data along with data on expected determinants of exposure to construct statistical models which can then be applied to estimate exposures for the entire cohort (Nieuwenhuijsen et al., 2006). In this investigation, we explored the applicability of such an approach in estimating UFP exposures in homes, schools, and transportation environments. In doing so, our primary objectives were to characterize UFP exposures in these environments and to develop statistical models to estimate such exposures based on readily available information such as home/school characteristics and ambient weather data. As a secondary objective, we performed small-scale evaluations of these models to determine which environments may be most suitable for UFP exposure modeling in population-based studies.

1.1 PREFACE TO THESIS

The thesis work is presented as four manuscripts. Manuscript A is a literature review discussing toxicological and epidemiological evidence related to UFPs and asthma. Common indoor UFP sources, particle composition, and formation mechanisms are discussed as well as findings from studies exploring other potential health effects of UFP exposures. The version of Manuscript A presented below differs slightly from the original version published in *Indoor Air* as it has been updated to include more recent findings. Manuscript B describes a cross-sectional survey of residential UFP exposures according to the type of home heating system. This manuscript also differs slightly from the original version published in the *Journal of Exposure Science and Environmental Epidemiology* as it has been extended to include a section on the development and evaluation of an exposure assessment model for UFPs in homes. Manuscript C has been accepted for publication in the *Journal of Exposure Science and Environmental Epidemiology* and reports findings from an 8-month survey of UFP exposures in transportation environments. In addition, Manuscript C presents predictive models for UFP exposures while walking, riding in a public transit bus, and while riding in an automobile. Manuscript D has been accepted for publication in *Environmental Research,* and explores determinants of UFP exposures in school classrooms during the winter months and presents a model to estimate such exposures.

2. LITERATURE REVIEW

MANUSCRIPT A

INDOOR ULTRAFINE PARTICLES AND CHILDHOOD ASTHMA: EXPLORING A POTENTIAL PUBILC HEALTH CONCERN

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Abstract

Exposure to airborne particulate matter has a negative effect on respiratory health in both children and adults. The ultrafine fraction of particulate air pollution is of particular interest owing to its increased ability to cause oxidative stress and inflammation in the lungs. We reviewed the literature, and to date findings suggest that ultrafine particles (UFPs) may play an important role in triggering asthma symptoms. Furthermore, we believe that indoor UFP exposures may be particularly important because people spend the majority of their time indoors where sources of these contaminants are often present. While several epidemiological studies have examined the respiratory effects of ambient UFP exposures, the relationship between indoor UFP exposures and childhood asthma has yet to be examined in clinical or epidemiological studies. Therefore, the aim of this article is to provide a general review of UFP toxicity as related to childhood asthma in order to draw attention to a potentially important public health concern.

Practical Implications

A number of indoor sources of UFPs have been identified, but the health effects of indoor UFP exposures remain largely unexplored. The potential respiratory effects of such exposures seem most concerning because these particles are known to cause oxidative stress and inflammation in the lungs. Subsequently, indoor UFP exposures may contribute to the exacerbation of asthma symptoms in susceptible individuals. This paper provides a review of UFP toxicity as related to childhood asthma, and to date evidence suggests that further investigation into the respiratory effects of indoor UFP exposures is warranted.

Introduction

Asthma is the most common childhood disease in the developed world, and is characterized by bronchial hyperresponsiveness, chronic airway inflammation, recurrent wheezing, and mucus hyper-secretion (Busse & Lemanske, 2001; Clark et al., 1999). Asthma onset is governed by complex interactions between individual genetic susceptibility and environmental exposures, and as such, indoor exposures are important because young children spend the majority of their time exposed to indoor air. While biological risk factors such as dust mite and cockroach allergens are known triggers of allergic asthma in some individuals (Gold, 2000), evidence in support of previously suspected indoor chemical pollutants such as volatile organic compounds and nitrogen dioxide, while not to be discarded, remains inconsistent (Weichenthal et al., 2007). The degree to which UFPs contribute to bronchial hyper-reactivity in asthma sufferers is not yet clear, but their ability to promote an allergic immune response has been demonstrated in several animal studies (Granum et al., 2000; Granum et al., 2001; Lambert et al., 2003a; Lambert et al., 2003b). However, uncertainty remains as to whether UFPs actually cause asthma in genetically susceptible individuals, or simply exacerbate symptoms in those already affected with this disease. Nevertheless, UFPs are attractive targets in future investigations of indoor risk factors for childhood asthma because toxicological evidence suggests that such a relationship is plausible.

Formation of Ultrafine Particles

Ultrafine particles are generally defined as those particles with diameters less than 100 nm. In the ambient environment, UFPs originate primarily from vehicle emissions (Fine et al., 2004; Levy et al., 2003; Morawska et al., 1999) and nucleation events involving gas-to-particle conversions (Korhonen et al., 2004; Kulmala et al., 2004). The formation of UFPs by gas-to-particle conversions depends on the concentration of compounds such as sulfur dioxide in the atmosphere, which when oxidized to sulfuric acid by photochemical reactions or oxidant gases (e.g. ozone, hydroxyl and nitrate radicals), combines with water (or ammonia and water) to form new particles through binary (H_2SO_4-H_2O) or ternary (H_2SO_4-NH_3-H_2O) nucleation (Korhonen et al., 2004; Kulmala et al., 2004). These particles then grow in size as nuclei coagulate and low volatility gaseous compounds such as sulfuric acid, ammonia, water, and water-soluble and water-insoluble organic compounds condense on the particle surface (Korhonen et al., 2004). Indeed, ambient UFP number concentrations have been shown to increase with elevated sulfur dioxide concentrations (Jeong et al., 2004), and in the Los Angeles basin photochemical reactions have been identified as a source of ambient UFPs in the afternoon hours (Kim et al., 2002). However, the exact mechanism of this process remains unclear and nucleation events independent of sulfuric acid and ammonia may be possible (Korhonen et al., 2004; Kulmala et al., 2004). Regardless of the mechanism, ambient UFP formation rates by gas-to-particle conversions are estimated to be in the range of 0.01-10 $cm^{-3}s^{-1}$ for 3 nm particles, with rates up to 100 $cm^{-3}s^{-1}$ estimated for urban areas (Kulmala et al., 2004). Growth rates for these particles typically range from 1-20 nmh^{-1} depending on temperature (growth rates are slower in the winter than in the summer) and the availability of condensable vapors (Kulmala et al., 2004). For

vehicles, UFP emissions rates of 11.7-13.5 x 10^{14} particles/km and 3.9 x10^{14} particles/km have been estimated for highway (80-120 km/h) and urban driving (0-50 km/h), respectively (Imhof et al., 2005).

Common sources of indoor UFPs include home cooking and heating systems, but other sources such as tobacco smoke, burning candles, vacuuming, natural gas clothes dryers, and other household activities also contribute to indoor UFP levels (Table 1) (Abt et al., 2000; Afshari et al., 2005; Dennekamp et al., 2001; He et al., 2004; Hussein et al., 2005; Li et al., 1993; Matson, 2005; Wallace, 2000; Wallace et al., 2004a; Wallace, 2005; Wallace & Howard-Reed, 2002). In addition to these sources, ozone/terpene reactions may also serve as a source of indoor UFPs. In an experimental study, Weschler & Shields (1999) introduced the terpene d-limonene (used as a citrus scent in cleaning products) into an office and detected up to a 10-fold increase in the concentrations of 100 nm particles compared to an office with no d-limonene added. In this investigation, particle concentrations were reported to track indoor ozone concentrations (from outdoor-to-indoor transport only) with an approximate 30 minute lag period between ozone peaks and particle peaks (Weschler & Shields, 1999). However, the particle sizes examined in this investigation were generally larger than UFPs, and thus further research is required to determine the role of ozone/terpene reactions in generating indoor UFPs. Indeed, some research suggests that the oxidation products of ozone/terpene reactions may be of more concern than UFPs produced by this process because a significant increase in blink frequency (a measure of eye irritation) has been associated with exposure to limonene oxidation products in the absence of UFPs (Kleno & Wolkoff, 2004). However, it is too early to draw any conclusions regarding the toxicity of UFPs produced by ozone/terpene reactions, particularly in office environments

where sources of ozone are common (Lee et al., 2001). Whatever their emission source, UFPs are removed from indoor air primarily by Brownian diffusion with minimum deposition rates observed for particle diameters of approximately 100 nm (Riley et al., 2002). While the use of forced-air circulation and in-duct filters in the home can also increase indoor UFP deposition rates (Wallace et al., 2004b), UFPs are not removed as efficiently as larger particles by electrostatic precipitators in central air heating/cooling systems (Huang & Chen, 2002). Some evidence indicates that the removal efficiency of UFPs may be increased by replacing the collector electrode in electrostatic precipitators with a wire screen (Alonso & Alguacil, 2002); but clogging of this screen may then become an issue.

Composition of Ultrafine Particles

While the small size of UFPs precludes them from contributing greatly to the overall mass concentration of airborne particulate matter, they are the predominant particle size by number and have a very large surface area per unit mass which allows for greater adsorption of toxic chemicals (Li et al., 2003a). Studies of ambient UFPs suggest that these particles are primarily composed of carbonaceous materials, with a small portion of their mass made up of components such as sulphate, ammonium, nitrate, and various metals (Hughes et al., 1998; Pakkanen et al., 2001; Lin et al., 2005; Ntziachristos et al., 2007). Although the chemical composition of UFPs generated in residential environments remains largely unexplored, some evidence indicates that indoor UFPs may contain potentially harmful compounds. A recent risk assessment of exposure to indoor aerosols during Chinese cooking with a gas stove suggests that long-term exposure to such aerosols may have adverse health effects owing to the increased metal content of particles produced during cooking (See & Balasubramanian, 2006). Metals

examined in this investigation included those with carcinogenic (As, Cd, Cr, and Ni) and non-carcinogenic (Al, Cr, and Mn) health effects, and on average the mass concentration of metals increased by a factor of 11 during cooking. In addition, 80% of particles produced during cooking in this study were UFPs, and on average particle number concentrations increased by a factor of 85 during cooking. Although this investigation was conducted in a food-stall type restaurant environment where the intensity and frequency of cooking exceeds that of residences, this study draws attention to the potentially hazardous composition of UFPs produced indoors. Indeed, other studies have confirmed the genotoxicity of heated rapeseed and soybean oil vapors produced during Chinese cooking (Qu et al., 1992), an effect that may be due to the presence of carcinogenic polycyclic aromatic hydrocarbons in cooking oil fumes (Li et al., 1994). The carcinogenic capacity of UFPs produced during cooking may depend on the type of cooking method however, as a Norwegian cohort study failed to detect a significantly increased risk of lung cancer among cooks (Kjaerheim & Andersen, 1993). Alternatively, the type of cooking fuel may also be important as Norwegian restaurants at the time of this study depended primarily on electricity for cooking and not natural gas (Kjaerheim & Andersen, 1993). In children, exposure to wood smoke has been associated with cough and wheeze (Honicky et al., 1985). However, other studies have failed to detect such effects (Maier et al., 1997; Tuthill, 1984). Nevertheless, we have identified wood stoves as a source indoor UFPs in homes depending on wood burning for heating (unpublished data), and since wood smoke is composed of a number of respiratory irritants such as formaldehyde, acrolein, nitrogen oxides, and sulfur dioxide (Larson & Koenig, 1994), it seems possible that indoor UFPs produced by wood stoves may contain such compounds.

Infiltration of Outdoor Ultrafine Particles

The degree to which outdoor particulate matter penetrates the indoor environment is expressed as a penetration factor, with a value of one indicating that external walls have no effect on the infiltration of outdoor particles. Penetration factor estimates in the range of 0.5 to 0.9 have been reported (Vette et al., 2001), and in general, penetration factors are greatest for fine particles ($PM_{2.5}$) and lower for coarse (PM_{10}) and ultrafine particles (Liu & Nazaroff, 2001; Long et al., 2001). Therefore, outdoor UFP measurements may not adequately reflect indoor UFP exposures, particularly those occurring during the winter months when home ventilation is poor or those produced by constantly repeating sources. Indeed, the work of Wallace and Howard-Reed (2002) indicates that the majority (50-80%) of all indoor UFPs are produced by indoor sources, and that these sources are present an estimated twenty-two percent of the time as compared to twelve and fourteen percent of the time for fine and coarse particles, respectively. In addition, a recent study suggests that indoor UFP exposures contribute most to cumulative exposure levels owing to the large amount of time people spend indoors (Vinzents et al., 2005). Therefore, evidence to date indicates that UFPs are common residential indoor air pollutants, and are thus available to trigger adverse respiratory effects in potentially susceptible individuals. Indeed, the biological plausibility of a relationship between UFP exposures and asthma is supported by a number of studies, and these studies are discussed next.

Ultrafine Particle Toxicology

In Vitro Studies

Oxidative stress contributes to the production of airway inflammation characteristic of asthma. Studies in cell-free systems indicate that UFPs promote the formation of reactive oxygen species (ROS) (Brown et al., 2001; Dick et al., 2003; Zheng et al., 1998), and that this effect may in turn depend on particle surface area (Koike & Kobayashi, 2006; Monteiller et al., 2007). In addition, some evidence indicates that UFPs generate more ROS than larger fine or course particles in alveolar epithelial and macrophage cells (Li et al., 2003a; Stone et al., 1998; Wilson et al., 2002). The importance of oxidative stress in the respiratory health effects of particulate matter is discussed extensively in a recent review (Li et al., 2003b), and the enhanced ability of UFPs to generate oxidative stress in the lungs may be due to their large surface area (Beck-Speier et al., 2001). Furthermore, UFPs may prolong the effects of other inhaled pollutants as they have been shown to impair phagocytosis by alveolar macrophages (Lundborg et al., 2001; Renwick et al., 2001). Phagocytosis is an important process in the removal of foreign materials from the lungs, and depends on the coordinated function of cell structures known as actin, myosin, and intermediate filaments which collectively form the cellular cytoskeleton. Cytoskeleton function in turn depends on intracellular calcium ion (Ca^{+2}) concentrations, with increased levels disrupting cytoskeletal function (Dalle-Donne et al., 2001). While it is not yet clear whether the uptake of UFPs into respiratory cells is dependent (Stearns et al., 2001) or independent of phagocytosis (Geiser et al., 2005), these particles have been shown to increase Ca^{+2} concentrations in macrophages, an effect not observed for larger particles (Brown et al., 2000; Brown et al., 2001; Brown et al., 2004; Stone et al., 2000). This finding is also important

because some transcription factors which are required for the expression of pro-inflammatory genes are themselves regulated by calcium. Indeed, in vitro studies have shown that UFPs can stimulate the expression of pro-inflammatory proteins in airway epithelial cells and alveolar macrophages (Drumm et al., 1999; Kim et al., 2005). Likewise, this effect may be stronger for UFPs than for larger particles (Brown et al., 2001). Interestingly, when compounds which block calcium entry into the cell or otherwise prevent calcium utilization are applied to rat or human alveolar macrophages, the ability of UFPs to inhibit phagocytosis and stimulate the expression of pro-inflammatory genes is prevented (Brown et al., 2004; Moller et al., 2005). Therefore, in vitro studies suggest that the respiratory toxicity of UFPs may be partially attributed to their ability to increase intracellular calcium levels, which in turn inhibits phagocytosis and promotes the activation of transcription factors for pro-inflammatory genes.

In asthmatic individuals, recurrent cycles of airway inflammation and repair can lead to structural changes in the airway wall which are collectively termed "airway remodeling" (Beckett & Howard, 2003; Lazaar & Panettieri, 2003). Airway wall thickening is one characteristic sign of airway remodeling, and some findings suggest that UFPs may contribute to this process (Tamaoki et al., 2004). A second characteristic of airway remodeling is epithelial damage, and at least one study indicates that UFPs may promote this effect by inhibiting tissue repair (Kim et al., 2003). As such, UFPs may not only contribute to the inflammatory processes characteristic of asthma, but may also promote the structural changes observed in the airways of asthmatic individuals.

In Vivo Studies

Asthma onset typically involves a shift in the balance of immune function from a cell-mediated immune response involving T-helper type 1 lymphocytes (Th1) to an antibody-mediated immune response involving T-helper type 2 (Th2) lymphocytes (Babu & Arshad, 2003). In general, this shift involves the development of an immunological memory to inhaled allergens through the production of specific immunoglobulin (IgE) antibodies; thus leaving individuals prone to airway inflammation upon repeated allergen exposures (Babu & Arshad, 2003). Interestingly, in vivo studies conducted by Lambert et al. (2003) indicate that UFP exposures may promote or enhance Th2 type immune responses following exposure to biological risk factors for childhood asthma such as respiratory syncytial virus (RSV). In one of these studies (Lambert et al., 2003a), RSV infected mice pre-exposed to ultrafine carbon black particles displayed significantly higher levels of the Th2 cytokine interleukin-13 (IL-13) in lung homogenate than mice exposed only to RSV. Cytokines are proteins that act as signaling molecules to regulate immune responses, and IL-13 acts in conjunction with other Th2 cytokines to promote a Th2 phenotype (Busse & Lemanske, 2001). In this study, pre-exposed mice also displayed significantly lower levels of interferon inducible protein mRNA, an early response chemokine produced by bronchial epithelial cells, macrophages, and neutrophils to induce a Th1 type immune response. Decreased levels of interferon-gamma, a second Th1 cytokine, were also observed in mice pre-exposed to ultrafine carbon black particles and in general these mice displayed more severe pulmonary inflammation. Since pre-exposure to UFPs did not significantly alter RSV replication or clearance in this study, the findings presented suggest that exposure to ultrafine carbon black particles prior to RSV infection promotes an allergic (Th2)

immune response. In fact, a reduction in Th1 cytokines was also observed in mice exposed only to ultrafine carbon black particles, thus suggesting a shift toward a Th2 phenotype due to particle exposure alone. The findings of Granum et al. (2001) support these results, and an earlier investigation suggests that the ability of UFPs to stimulate Th2 type immune responses may depend on particle number and surface area (Granum et al., 2000). Although further investigation is required, the potential ability of UFPs to promote a Th2 type immune response may be one method by which indoor UFP exposures promote childhood asthma.

In a related study, Lambert et al. (2003b) administered ultrafine carbon black exposures following RSV infection and found that RSV infected mice that were also exposed to ultrafine carbon black particles displayed increased numbers of inflammatory markers in bronchoalveolar lavage fluid including macrophages, lymphocytes, neutrophils, and total protein levels without a change in viral titer and clearance. In addition, UFP exposures in this study increased RSV-induced airway hyper-responsiveness to methacholine, a compound commonly used to trigger airway hyper-reactivity. Likewise, the adjuvant effects of UFP exposures on allergic lung inflammation were demonstrated in a more recent study which observed a significant increase in airway inflammation in sensitized mice exposed to UFPs twenty-four hours before allergen challenge (Alessandrini et al., 2006). In this study, UFP exposures occurring after allergen exposure caused only moderate effects (Alessandrini et al., 2006), and some findings suggest that co-exposure to UFPs and allergen may induce a greater inflammatory response than allergen alone (de Haar et al., 2006; Inoue et al., 2006).

Other in vivo studies also suggest that a relationship between indoor UFP exposures and asthma is plausible. For example, UFPs have been shown to generate oxidative stress in the

lungs of experimental animals (Zhou et al., 2003a; Zhou et al., 2003b; Kaewamatawong et al., 2006) and to cause more epithelial damage than fine particles of the same composition (Renwich et al., 2004; Kaewamatawong et al., 2005). Likewise, several studies indicate that UFPs generate a pronounced inflammatory response in the lungs (Afaq et al., 1998; Brown et al., 2001; Dick et al., 2003; Gilmour et al., 2004a; Gilmour et al., 2004b; Li et al., 1996; Oberdorster et al., 1994; Shwe et al., 2005; Zheng et al., 1998; Hahn et al., 2005; André et al., 2006), and this effect may be correlated with particle surface area (Brown et al., 2001; Hohr et al., 2002; Nygaard et al., 2004; Oberdorster et al., 1994; Stoeger et al., 2006). Consistent with these findings is the fact that UFPs with greater surface areas have been shown to induce more inflammation and generate increased levels of ROS (Dick et al., 2003; Renwich et al., 2004). However, particle size and composition likely also play an important role in determining overall toxicity. Furthermore, some evidence suggests that abrupt increases in UFP exposures may cause greater inflammatory effects than exposure at a constant level (Hahn et al., 2005).

UFPs are not efficiently phagocytized in vivo (Kreyling et al., 2002; Oberdorster et al., 1992; Oberdorster et al., 1994; Renwich et al., 2004; Semmler et al., 2004), and once inhaled these particles are widely distributed throughout all major lung compartments and cells (Geiser et al., 2005). Consistent with in vitro studies suggesting a role for UFPs in airway remodeling, a recent study suggests that exposure to ultrafine carbon black particles may lead to alveolar wall thickening (Chang et al., 2005). This same study also indicates that reactive oxygen species produced by UFPs may increase the permeability of the alveolar-capillary barrier. This is an important finding with respect to asthma because increased permeability of the alveolar-capillary

barrier may allow UFPs to access smooth muscle cells and directly influence airway hyperresponsiveness.

In general, both in vitro and in vivo studies tend to support the biological plausibility of a potential relationship between indoor UFP exposures and childhood asthma. In vitro studies suggest that UFPs increase intracellular calcium levels in alveolar macrophages, thus leading to the production of inflammatory cytokines by these cells. In vivo studies confirm the results of in vitro studies, and suggest further that exposure to UFPs may promote a Th2 type immune response. Li et al. 2003b provide an explanation for this effect, as it is their hypothesis that oxidative stress caused by inhaled particulate matter promotes the expression of specific protein receptors on antigen presenting cells, which in turn enhances Th2 type immune responses and allergic inflammation by promoting interaction between antigen presenting cells and Th2 lymphocytes.

Experimental Studies in Humans

Experimental studies of UFP exposures in humans have been conducted mainly in adult subjects and have focused primarily on particle deposition in the lungs. For UFPs, pulmonary deposition is governed primarily by diffusion (Oberdörster et al., 2005), with the majority of 20-100 nm particles deposited in respiratory bronchioles and alveoli (Bolch et al., 2001; Lazardis et al., 2001). However, some evidence suggests that UFP hygroscopicity (the ability to grow by water condensation) may also influence particle deposition, with greater deposition observed for hydrophobic particles (Löhdahl et al., 2007). Regardless, evidence to date suggests that UFPs are efficiently deposited in the human airway (Wilson et al., 1985; Jaques & Kim, 2000; Wiebert et al., 2006), and that deposition is similar for healthy young and elderly subjects under similar

exposure conditions (Kim & Jaques, 2005). However, UFP deposition is greater in asthmatic subjects, with exercise and decreasing particle size acting to further increase the number of UFPs retained in the lung (Chalupa et al., 2004; Daigle et al., 2003; Frampton et al., 2004; Jaques & Kim, 2000; Wilson et al., 1985). Likewise, adults with chronic obstructive pulmonary diseases may also receive an increased dose of inhaled UFPs (Brown et al., 2002).

Experimental studies of controlled UFP exposure suggest that inhalation of ultrafine zinc oxide fume leads to increased pulmonary inflammation (Fine et al., 1997; Kuschner et al., 1995; Kuschner et al., 1997a). However, this same effect was not observed for ultrafine magnesium oxide (Kuschner et al., 1997b), and thus UFP composition may be an important determinant of the biological effects of exposure. A study of ultrafine carbon exposure also failed to detect a difference in airway inflammation between healthy and asthmatic subjects exposed to UFPs (Pietropaoli et al., 2004). However, this study did observe small airway dysfunction and impaired alveolar gas exchange in normal subjects exposed to UFPs. A more recent study failed to detect a significant difference in inflammatory markers in induced sputum in healthy adult subjects exposed for two hours to an equal mass concentration of fine and ultrafine zinc oxide particles (Beckett et al., 2005). The number and mass deposition fractions for UFPs in this study were very high however, at seventy-five and seventy-eight percent respectively. Increased pulmonary inflammation has been observed in studies of controlled exposure to diesel exhaust particles, which are primarily composed of UFPs (Nightingale et al., 2000; Salvi et al., 1999; Salvi et al., 2000). However, the findings of Holgate et al. (2002) suggest that this effect may not be greater for asthmatic subjects relative to healthy controls. Positive results were reported in a recent study investigating the ability of UFPs to cause oxidative DNA damage (Vinzents et al.,

2005). Briefly, using personal UFP exposure data from the breathing zones of healthy non-smoking men and women, this study identified cumulative indoor and outdoor UFP exposures as significant independent predictors of oxidative DNA damage in mononuclear cells isolated from venous blood. Importantly, this study suggests that real-life indoor UFP exposures such as those experienced during cooking can result in oxidative damage in human systems. While oxidative damage in the respiratory tract was not investigated in this study, it seems likely that a similar effect may be observed in these cells as they are often first to encounter such exposures.

While several experimental studies have reported increased pulmonary inflammation in response to UFP exposure, others have failed to do so. As such, findings of controlled UFP exposure studies are somewhat inconsistent. This variation may be partially attributed to the different doses and particle compositions employed by these studies, as well as differences in exposure duration and the amount of time between exposure and the assessment of health effects. Also, it should be noted that the short-term exposure paradigms employed in these studies may not reflect real-life exposures or the physiological responses of children. Importantly, however, experimental studies in humans indicate that UFPs are efficiently deposited in the airway and that typical indoor exposures can have a measurable impact on oxidative stress in the body. As such, these studies support the biological plausibility of a potential relationship between indoor UFP exposures and childhood asthma. While epidemiological studies have yet to examine the respiratory effects of indoor UFPs exposures, several have investigated the respiratory effects of ambient UFP exposures and these are discussed next.

Population Studies of Ambient UFP Exposures

Epidemiological studies of the respiratory health effects of UFP exposures have focused primarily on ambient exposures in adult populations, with few studies considering the effects of ambient childhood exposures, and no studies examining the effects of indoor UFP exposures. In asthmatic adult populations, negative associations between peak expiratory flow rate and number concentrations of UFPs have been reported, with this effect being stronger for UFPs than for larger particles (Penttinen et al., 2001a; Peters et al., 1997). However, one study reported a stronger negative correlation between the number of fine particles and peak expiratory flow rate in adult asthmatics than that for UFPs (Penttinen et al., 2001b). Nevertheless, ambient fourteen-day mean UFP number concentrations have been associated with asthma medication use in adult asthmatics as well as wheezing (Odds Ratio=1.26, 95% Confidence Interval:1.08-1.48), waking up with breathing problems (OR=1.26, 95% CI: 1.13-1.41), shortness of breath (OR=1.24, 95% CI: 1.11-1.40), phlegm (OR=1.11, 95% CI: 0.99-1.25), and cough (OR=1.20, 95% CI: 1.06-1.35) (von Klot et al., 2002). One study of the acute respiratory effects of UFP exposures in adult asthmatic subjects did measure indoor UFP number concentrations in addition to outdoor levels (Osunsanya et al., 2001). However, these measurements were collected in an empty laboratory with no indoor sources for the purpose of comparing indoor and outdoor levels, and were not used to estimate actual exposures. Instead, outdoor UFP measurements were used for exposure assessment, and this study failed to detect an association between peak flow rate and ambient UFP number concentrations. Likewise, single site outdoor monitoring was also used to evaluate the effects of ambient particulate matter on peak expiratory flow in asthmatic children (Pekkanen et al., 1997; Tiittanen et al., 1999). While variations in peak expiratory flow were more strongly

associated with UFPs in one of these studies (Pekkanen et al., 1997), in general the observed effect of ambient UFPs was not greater than that for larger particles. However, separating the independent effects of different sized particles in these studies was difficult owing to their high inter-correlations (Pekkanen et al., 1997; Tiittanen et al., 1999), and Pekkanen et al. (1997) noted further that outdoor measurements may provide poor estimates of actual UFP exposures in children owing to time spent indoors.

Cardiovascular effects of UFP exposures

In addition to their potential respiratory effects, some evidence suggests that UFPs might also play a role in triggering adverse cardiovascular outcomes (Frampton et al., 2001; Delfino et al., 2005). For example, experimental studies in animals and humans indicate that inhaled UFPs reach the systemic circulation soon after exposure and may alter autonomic activity (Nemmar et al., 2001; Nemmar et al., 2002; Elder & Oberdörster, 2006; Shimada et al., 2006). Specifically, changes in heart rate have been observed in rats exposed to UFPs (Elder et al., 2007; Nemmar et al., 2007), and significant increases in systolic and diastolic blood pressure as well as heart rate have been observed among patients with reduced lung function for each 10 000 cm^{-3} increase in personal UFP exposure (Chuang et al, 2005). Furthermore, exercise at a location with high ambient UFP levels (143 501 ± 58 565 cm^{-3}) relative to low levels (5309 ± 1942 cm^{-3}) has been associated with significant vasoconstriction of the brachial artery and reduced reperfusion rate to the forearm muscle among healthy, non-smoking male adults (Rundell et al., 2007). While these effects may be of little consequence to healthy subjects, similar exposures could have a considerable impact on susceptible populations such as individuals suffering from cardiovascular disease.

Additional evidence for a potential relationship between UFPs and adverse cardiovascular effects comes from studies which suggest that UFPs may promote platelet aggregation and coagulation. For example, in vitro evidence suggests that UFPs promote the expression of genes related to coagulation (Karoly et al, 2007), and effects including platelet accumulation (Khandoga et al., 2004) and shorting of bleeding times (Nemmar et al., 2007) have been observed in animal studies following UFP exposure. In one of these studies, systemically administered UFPs also triggered pulmonary inflammation suggesting that UFPs may continue to have adverse respiratory effects after translocation from the lung to the systemic circulation (Nemmar et al., 2007). In humans, controlled exposure to wood smoke consisting primarily of UFPs resulted in increased levels of serum amyloid A, a cardiovascular risk factor (Johnson et al., 2004), as well as changes in the factor VIII/von Willebrand factor ratio consistent with procoagulatory effects (Barregard et al., 2006). In addition, ambient UFPs have been associated with cardio-respiratory mortality (Stölzel et al., 2006), stroke mortality (Kettunen et al., 2007), and hospital readmissions among myocardial infarction survivors (von Klot et al., 2005). Furthermore, significant positive relationships have been detected between ambient UFP counts and CD40-ligand (a glycoprotein released from platelets which promotes blood clot formation) as well as serum fibrinogen levels (a blood clotting factor) among male patients with coronary heart disease in Erfurt, Germany (Rückerl et al., 2007), and elderly subjects in Boston, Massachusetts, respectively (Zeka et al., 2006). In the Boston cohort, the relationship between UFPs and serum fibrinogen levels tended to be greatest among older, more obese subjects (Zeka et al., 2006). More in-depth reviews of the potential health effects of UFPs outside the lung are available elsewhere (Risom et al., 2005; Elder & Oberdörster, 2006; Peters et al., 2006).

Conclusions

Exposure to airborne particulate matter remains an important public health concern. In particular, the potential health effects of UFP exposures seem troubling as a number of animal studies suggest that these particles may promote airway inflammation and/or adverse cardiovascular effects as well as allergic immune responses characteristic of asthma. In addition, experimental studies in humans indicate that these particles are efficiently deposited in the lungs, and that typical indoor exposures can cause oxidative stress in the body. Unfortunately, however, the potential health effects of indoor UFP exposures remain largely unexplored and future studies should address this concern as evidence to date supports the biological plausibility of a relationship between indoor UFP exposures and respiratory as well as cardiovascular illness.

TABLES

Table 1: Indoor Sources of Ultrafine Particles

Study	Instrumentation	Indoor Source	Indoor UFP Measurement
Wallace et al., 2004a	Differential Mobility Analyzer (DMA) and Condensation Particle Counter (CPC)	Frying on a gas stove	Mean number concentration of 1.0×10^5 cm^{-3}
Abt et al., 2000	Scanning Mobility Particle Sizer (SMPS)	Oven cooking	Peak size-dependent number concentration range between $1.1\text{-}1.3 \times 10^4$ cm^{-3}
Wallace, 2000	SMPS	Boiling Water	Size profile of UFPs presented. Peak number concentration of 400 cm^{-3} for 10 nm particles
		Gas Burners	Size profile of UFPs presented. Peak number concentration of 700 cm^{-3} for 10 nm particles
		Electric Toaster Oven	Size profile of UFPs presented. Peak number concentration of 650 cm^{-3} for 10 nm particles
		Sautéing	Size profile of UFPs presented. Peak number concentration of 200 cm^{-3} for 43 nm particles
		Deep Frying Tortillas	Size profile of UFPs presented. Peak number concentration of 1800 cm^{-3} for 74 nm particles
		Frying Veggie Burgers	Size profile of UFPs presented. Peak number concentration of 400 cm^{-3} for 35 nm particles
Afshari et al., 2005	CPC	Frying on an electric stove	Peak number concentration of 1.51×10^5 cm^{-3}
		Portable Electric Heater	Peak number concentration of 1.16×10^5 cm^{-3}
		Electric Radiator	Peak number concentration of 2.18×10^5 cm^{-3}
		Electric Stove Alone	Peak number concentration of 1.11×10^5 cm^{-3}
		Cigarettes	Peak number concentration of 2.13×10^5 cm^{-3}
		Wax Candle	Peak number concentration of 2.41×10^5 cm^{-3}
		Air Freshener Spray	Peak number concentration of 3.0×10^4 cm^{-3}
		Vacuum Cleaner	Peak number concentration of 2.1×10^4 cm^{-3}

Table 1. *Continued*

Study	Instrumentation	Cooking /Heating Source	Indoor UFP Measurement
Dennekamp et al., 2001	SMPS	Gas rings only	Peak number concentration of 2.6 x 10^4 cm^{-3} for 1 ring and 14.6 x 10^4 cm^{-3} for four rings
		Electric Rings	Peak number concentration of 9.4 x 10^4 cm^{-3} for 1 ring and 1.1 x 10^5 cm^{-3} for four rings
		Gas Oven	Peak number concentration of 1.3 x 10^5 cm^{-3}
		Electric Oven	Peak number concentration of 3.0 x 10^4 cm^{-3}
		Boil water on Gas Stove	Peak number concentration of 1.3 x 10^5 cm^{-3}
		Stir Fry	Peak number concentrations of 1.4 x 10^5 cm^{-3} for the gas stove and 1.1 x 10^4 cm^{-3} for the electric stove
		Frying Bacon	Peak number concentrations of 5.9 x 10^5 cm^{-3} for the gas stove and 1.6 x 10^5 cm^{-3} for the electric stove
		Grill Only	Peak number concentrations of 1.0 x 10^5 cm^{-3} for the gas stove and 7.7 x 10^4 cm^{-3} for the electric stove
		Grill Toast	Peak number concentrations of 1.4 x 10^5 cm^{-3} for the gas stove and 1.3 x 10^5 cm^{-3} for the electric stove
		Grill Bacon	Peak number concentrations of 4.1 x 10^5 cm^{-3} for the gas stove and 5.3 x 10^5 cm^{-3} for the electric stove
He et al., 2004	CPC	Electric stove	Peak median number concentration of 1.8 x 10^5 cm^{-3}
		Fan heater	Peak median number concentration of 8.7 x 10^4 cm^{-3}
		Washing Machine	Peak median number concentration of 1.1 x 10^4 cm^{-3}
Wallace, 2005	SMPS	Vented Gas Clothes Dryer	Peak number concentration of 1 x 10^5 cm^{-3}

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2.1 PREFACE TO MANUSCRIPT B

Findings to date support the biological plausibility of relationship between UFP exposures and adverse cardiovascular and respiratory outcomes. As such, the potential health effects of indoor UFP exposures are of particular interest owing to the fact that people spend the majority of their time indoors. In cold climates, the potential impact of home heating systems on indoor UFP exposures is of concern because these systems are active for many months of the year. Unfortunately, however, little is known about the impact of home heating systems on UFP exposures as limited research has focused on the development of exposure assessment models for UFPs in homes. To address these issues, we conducted a cross-sectional survey of indoor UFP exposures in Canadian homes during the winter months. In doing so, we compared indoor UFP levels between homes with four different types of heating systems (electric baseboard heaters, wood stoves, and forced-air oil/natural gas furnaces) and constructed an exposure assessment model based on determinant information collected using a questionnaire as well as indoor air quality measures such as temperature and relative humidity. A predictive model was developed using data from a sub-set of homes and this model was then tested in the remaining homes to mimic the process likely to be applied in large population-based studies. For comparison, a "final" model was also developed which was based on data collected from all homes combined. What follows is a detailed manuscript describing the findings of this investigation.

3. MANUSCRIPT B

INDOOR ULTRAFINE PARTICLE EXPOSURES AND HOME HEATING SYSTEMS: A CROSS-SECTIONAL SURVEY OF CANADIAN HOMES DURING THE WINTER MONTHS

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Abstract

Exposure to airborne particulate matter has a negative effect on respiratory health in both children and adults. Ultrafine particle (UFP) exposures are of particular concern owing to their enhanced ability to cause oxidative stress and inflammation in the lungs. In this investigation, our objective was to examine the contribution of home heating systems (electric baseboard heaters, wood stoves, forced-air oil/natural gas furnace) to indoor UFP exposures. We conducted a cross-sectional survey in 36 homes in the cities of Montréal, Québec, and Pembroke, Ontario. Real-time measures of indoor UFP concentrations were collected in each home for approximately 14 h, and an outdoor UFP measurement was collected outside each home prior to indoor sampling. A home-characteristic questionnaire was also administered, and air exchange rates were estimated using carbon dioxide as a tracer gas. Average UFP exposures of 21,594 cm^{-3} (95% Confidence Interval: 14,014, 29,174) and 6660 cm^{-3} (95% CI: 4339, 8982) were observed for the evening (1600-2400) and overnight (2400-800) hours respectively. In an unadjusted comparison, overnight baseline UFP exposures were significantly greater in homes with electric baseboard heaters as compared to homes using forced-air oil or natural gas furnaces, and homes using wood stoves had significantly greater overnight baseline UFP exposures than homes using forced-air natural gas furnaces. However, in multivariable models, electric oven use (β=12,253, 95% CI: 3524, 20,982), indoor relative humidity (β=1136, 95% CI: 372, 1899) and indoor smoking (β=18,192 , 95% CI: 2073, 34,311) were the only significant determinants of mean indoor UFP exposure, whereas air exchange rate (β=4351, 95% CI: 1507, 7195) and each 10,000 cm^{-3} increase in outdoor UFPs (β=811, 95% CI: 244, 1377) were the only significant determinants of overnight baseline UFP exposures. In a small-scale evaluation of model performance, a modest correlation was observed between measured and predicted UFP

exposures in homes (r = 0.54). In general, our findings suggest that home heating systems are not important determinants of indoor UFP exposures and that modeling short term indoor UFP levels may be difficult owing to the transient nature of UFP emissions indoors.

Introduction

Ultrafine particles (UFPs) have diameters less than 100 nanometers (nm), and while they contribute very little to airborne particle mass, they are the predominant particle size by number (Donaldson et al., 2001; Oberdörster et al., 2005). In recent years, increased attention has focused on the respiratory effects of UFPs as animal studies have consistently demonstrated their ability to generate oxidative stress and inflammation in the lungs (Oberdörster et al., 1994; Li et al., 1996; Afaq et al., 1998; Zheng et al., 1998; Brown et al., 2001; Dick et al., 2003; Zhou et al., 2003a; Zhou et al., 2003b; Gilmour MI et al., 2004; Gilmour PS et al., 2004; Shwe et al., 2005). Several studies suggest that the large surface area of UFPs is an important determinant of their ability to cause airway inflammation (Oberdörster et al., 1994; Brown et al., 2001; Hohr et al., 2002; Nygaard et al., 2004), with a recent study reporting a threshold dose of 20 cm^2 for acute lung inflammation in mice (Stoeger et al., 2006). However, the chemical composition of UFPs likely also plays a role in determining their overall toxicity (Ovrevik and Schwarze, 2006).

Ultrafine particles are efficiently deposited in the human airway (Wilson et al., 1985; Jaques and Kim, 2000; Kim and Jaques, 2005), with the majority of 20-100 nm particles depositing in the respiratory bronchioles and alveoli (Bolch et al., 2001; Lazardis et al., 2001). People with asthma or chronic obstructive pulmonary disease may be particularly susceptible to the respiratory effects of UFPs, as deposition is greater in these individuals (Brown et al., 2002; Chalupa et al., 2004). Indeed, ambient UFP concentrations have been associated with a decrease in peak expiratory flow rate (Penttinen et al., 2001; Peters et al., 1997) as well as wheezing, shortness of breath, and cough in asthmatic adult populations (Von Klot et al., 2002). Similar investigations have been conducted in populations of asthmatic children (Pekkanen et al., 1997; Tiittanen et al., 1999), but separating the independent effects of different sized particles was

difficult in these studies owing to their high inter-correlations. Nevertheless, variations in peak expiratory flow rates were more strongly associated with ambient UFP concentrations in one of theses studies relative to larger particles (Pekkanen et al., 1997). Recently, UFP exposures were shown to contribute to oxidative DNA damage in healthy adults, with indoor exposures contributing most to cumulative exposure levels due to the large amount of time people spend indoors (Vinzents et al., 2005). Therefore, future population-based studies interested in the respiratory effects of UFPs may need to include indoor measures of UFP exposure to capture an accurate depiction of cumulative exposure profiles.

Indoor sources of UFPs have been investigated in a number of studies, and include cooking systems, portable heaters, burning candles, tobacco smoke, natural gas clothes dryers, and others (Li et al., 1993; Abt et al., 2000; Wallace, 2000; Dennekamp et al., 2001; Wallace and Howard-Reed, 2002; Morawska et al., 2003; He et al., 2004; Wallace et al., 2004; Afshari et al., 2005; Hussein et al., 2005; Matson, 2005; Wallace, 2005). However, studies to date have generally been conducted in 15 or fewer homes and have not compared indoor UFP exposures according to the type of home heating system. Such a comparison is warranted as heating systems such as electric radiators have been identified as a source of indoor UFPs (Afshari et al., 2005), and are often active for many months of the year. To address this issue, we conducted a cross-sectional survey of indoor UFP exposures in 36 residences during winter 2006. Our primary objective was to compare indoor UFP exposures between homes with electric baseboard heaters, wood stoves, forced-air natural gas furnaces, and forced-air oil furnaces as these systems are most common in Canadian homes (Natural Resources Canada 1994, 2000). Although sources such as cooking were expected to produce greater indoor UFP numbers, we expected home heating systems to have a larger influence on overnight exposures because these systems

are generally the only potential sources that are active during this time period. Specifically, we expected home heating systems to play a role in determining baseline UFP exposure levels during the overnight hours, with electric baseboard heaters and wood stoves contributing most owing to the exposed nature of the heating elements on these types of systems.

Methods

Home Selection and Locations

This study was conducted in 30 single-family homes and 6 town-house apartments between the months of December 2005 and March 2006. Twenty-five single-family homes were located in Pembroke, Ontario, 4 single-family homes were located in small towns surrounding Montréal, Québec, and 1 single family home and 6 town-house apartments were located in Montréal, Québec. Homes were identified opportunistically and through the distribution of an advertisement in the form of a brochure in autumn of 2005. In the brochure (Appendix 2), interested participants were asked to telephone or email a researcher and were telephoned in return to schedule an appointment for in-home sampling and questionnaire completion. All participants also signed an informed consent form (Appendix 3). The primary selection criteria was the type of home heating system, and in total thirty-eight volunteers expressed interest in study participation. We were unable to visit 2 of these 38 homes for reasons of poor weather conditions and a death in the family. Of the remaining 36 homes, 10 relied primarily on a forced-air natural gas furnace for heat, 10 relied on a forced-air oil furnace, 9 relied on electric baseboard heaters, and 7 seven relied on a wood stove. Five of the 7 wood stoves were the stand-alone type, which produce radiant heat for warmth, and two were forced-air wood furnaces.

In-Home Monitoring Scheme and Questionnaire

In-home monitoring was conducted over a 16 h time-period which included the evening cooking period (1600-2400) and overnight hours (2400-800) when other potential indoor sources of UFPs besides home heating systems were not expected to be active. One researcher visited each home once to set-up and another to collect instruments. During the first home visit, a home-

characteristic questionnaire was administered to participants to obtain information on the age and size of the home, vacuuming and dusting frequency, type of cooking system (electric or natural gas), types of cooking appliances used, use of a kitchen exhaust fan, number of smokers, burning candles, use of portable heaters, and use of a natural gas clothes dryer (Appendix 2). Mean outdoor temperature, relative humidity, and wind speed were also noted on each sampling day.

Instrumentation

Ultrafine particle concentrations (cm^{-3}) were monitored using TSI P-Trak 8525 UFP Counters. These are direct reading condensation particle counters capable of 8 h of continuous data logging before alcohol refill is needed. In addition, these instruments can detect particles as small as 20 nm at concentrations up to 5×10^5 cm^{-3}. In each home, one P-Trak was programmed to sample in the kitchen during the evening hours (1600-2400) and a second P-Trak was programmed to sample overnight (2400-800) in the main living area. A 1-min sampling interval was used for all continuous indoor UFP measurements, meaning that throughout the sampling period an indoor UFP measurement was recorded every minute and that the value recorded was the average UFP concentration over the previous minute. Before indoor UFP monitoring, a short outdoor UFP measurement was recorded for each home. Before collection, instrument readings were allowed to stabilize for approximately 2-min and then a 10-s average value for outdoor UFPs was recorded. Outdoor samples could not be collected for extended periods of time because the P-Trak does not function correctly below 0°C.

Continuous measures of indoor respirable particulate matter less than 4 μm (PM_4), temperature (as a sign of heating system activation), relative humidity, and carbon dioxide (used to estimate air exchange rates) were collected in the main living area of each home during the evening and overnight hours. Measurements for PM_4 were collected using a TSI DustTrak 8520

Aerosol Monitor whereas temperature, relative humidity, and carbon dioxide measures were collected using a TSI Q-Trak 8550. Indoor PM_4 was monitored to examine the potential correlation between respirable particulate matter and indoor UFPs, and this size range was selected because it represents the 50% cut-off point for particles capable of reaching the alveolar region of the lung. To examine the potential correlation between indoor UFPs and nitrogen dioxide, nitrogen dioxide levels were measured for 24 h in the main living area of homes relying on natural gas for heating using direct reading GasTec Color Dosimeter Tubes with a detection limit of 0.01 p.p.m.

Estimation of air exchange rate and home volume

Indoor air exchange rates (h^{-1}) (Ach) were estimated for each home using real-time measures of indoor carbon dioxide according to the following relationship:

$$Ach = \frac{\ln C_o - \ln C_t}{\Delta T} \qquad [1]$$

For this calculation, an initial indoor carbon dioxide concentration (C_o) was selected such that the time needed (ΔT) for a continuous linear decay to a lower concentration (C_t) was maximized throughout the sampling period. To correct for the background contribution of outdoor carbon dioxide, ambient concentrations were determined outside each home and subtracted from initial and final concentrations used in the above equation. Typically, air exchange rates were based on the decay of carbon dioxide in the main living area once residents had gone to their bedrooms for the night. Home volumes (m^3) were estimated by multiplying the reported total surface area of the home (m^2) by an assumed ceiling height of 2.4m (8 feet) per level.

Statistical Analysis

All parameter means, mean differences, standard deviations, 95% confidence intervals, R^2-values, Spearman's correlations, scatter-plots, and box-plots were generated using the commercially available statistical software package STATA version 9.1 (Statacorp, College Station, TX). We used multivariable models to estimate the effect of home heating system type on mean and baseline indoor UFP exposures while adjusting for factors such as home age, location, indoor/outdoor temperature, indoor/outdoor relative humidity, wind speed, home volume, air exchange rate, outdoor UFPs, indoor smoking, and electric oven use. A similar analysis was also conducted in which home heating system types were classified as either enclosed (forced-air oil furnaces, forced natural gas furnaces, forced-air wood stove) or exposed (electric baseboard heaters, stand-alone wood stoves). Spearman's correlation coefficients were calculated to estimate the correlations between independent variables. In the event of a substantial correlation ($|r| > 0.3$), three separate models were run (one model with each individual variable and one with both variables present) and if no important changes were observed both variables were explored in multivariable models. In all models, home heating system type, home location (urban or rural), indoor smoking, and electric oven use were treated as dichotomous variables whereas home age (years), home volume (m^3), indoor temperature (^oC), outdoor temperature (K), indoor/outdoor relative humidity (%), wind speed (km/h), air exchange rate (h^{-1}), and outdoor UFP concentration (cm^{-3}) were treated as continuous variables. Each home had only one type of heating system, and all homes located in Montréal, Québec, were classified as urban whereas all other homes were classified as rural. Real-time plots of indoor UFPs and temperature were produced using Trak Pro® software available from TSI (TSI Inc., Shoreview, MN, USA).

Bayesian Model Averaging (BMA) was used to select a model to predict UFP exposures in homes and was performed using the statistical software package R, version 2.4.0 (R Development Core Team, 2003). BMA is advantageous because model coefficients reflect a weighted average of all possible models weighted by the probability that each model is correct, thus accounting for model uncertainty (Kass and Raftery, 1995; Wasserman, 2000). In addition, Bayesian model selection has been shown to out-perform stepwise methods of model selection in making future predictions (Wang et al., 2004), as over-fitting is generally avoided. To mimic the process which may be applied in large-scale investigations, data from a sub-set of homes was used to develop a model and this model was then evaluated using data from the remaining homes. Specifically, data from the first 26 homes sampled (the first 5-8 homes in each group) were used to generate a model and this model was then tested in the remaining 10 homes. The correlation (r) between measured and predicted UFP exposures in homes was then assessed in a simple linear model and was calculated as the square root of the coefficient of determination (R^2). For comparison, a final model was also generated using data from all homes combined as the process of splitting the data described above does not lead to the "best model" owing to a reduction in sample size.

Results

Home Characteristics

A summary of home characteristics is shown in Table 1. In general, all homes used electricity for cooking and homes with electric baseboard heaters tended to be older, smaller, and contain fewer people but more smokers than homes with other types of heating systems. One home owned a natural gas clothes dryer but it was not used during the sampling period.

In-Home Quantitative Measures

In-home UFP monitoring data and values for other parameter measures are summarized in Table 2. Indoor UFPs were monitored in each home for an average duration of 14.1 h (SD = 2.5), and for all homes combined, average UFP exposures of 21,594 cm^{-3} (95% CI: 14,014, 29,174) and 6660 cm^{-3} (95% CI: 4339, 8982) were observed for the evening and overnight time periods, respectively. However, the difference between mean evening and overnight UFP exposures was significant only in rural homes (19,368 cm^{-3}, 95% CI: 11,043, 27,694), and not in urban settings (1364 cm^{-3}, 95% CI: -7752, 10,481) (Figure 1).

We observed no correlation between mean UFP exposures and burning candles (R^2=0.01), portable heater use (R^2=0.06), kitchen exhaust fan use (R^2=0.0), or vacuuming/dusting frequency (at least 1/week) (R^2=0.04). Similarly, we observed no correlation between either of the above variables and overnight baseline UFP exposures (R^2 <0.06). In addition, we observed no relationship between mean or baseline UFP exposures and outdoor temperature (R^2<0.08), relative humidity (R^2=0.0), or wind speed (R^2<0.03). Nitrogen dioxide was not detected (<0.01 p.p.m.) in any natural gas heated home. In unadjusted comparisons, there were no significant differences in mean indoor UFP exposures between homes with different heating systems, but overnight baseline exposures tended to be greater in homes using

either wood stoves or electric baseboard heaters. Specifically, homes with electric baseboard heaters had overnight baseline UFP concentrations that were on average 4104 cm^{-3} (95% CI: 1529, 6679) greater than homes with forced-air natural gas furnaces and 3448 cm^{-3} (95% CI: 680, 6216) greater than homes with forced-air oil furnaces. Wood heating homes had overnight baseline UFP concentrations that were on average 1469 cm^{-3} (95% CI: 304, 2634) greater than in homes with natural gas furnaces, but no other significant differences were observed. Distributions for mean and baseline UFP exposures in homes with different types of heating systems are shown in Figure 2.

No significant differences were observed for air exchange rates or mean PM_4 between homes with different heating systems. However, for all homes combined there was a significant correlation between mean indoor UFP and PM_4 exposure (R^2=0.53) (β= 155, 95% CI: 104, 206) (Figure 3). In addition, we observed significant correlations between overnight baseline UFP exposure and outdoor UFPs (R^2=0.39) (β= 0.11, 95% CI: 0.06, 0.16) and air exchange rate (R^2=0.28) (β= 5594, 95% CI: 2320, 8869) (Figure 4).

Spearman's Correlation Coefficients for Independent Variables in Multivariable Models

Spearman's correlation coefficients for the independent variables explored in multivariable models are shown in Table 3. Location and outdoor UFPs were significantly correlated, and as a result the location variable was dropped and outdoor UFP measurements alone were used to control for differences in outdoor UFP levels. Urban location and electric heating were also correlated, and when models including either electric heating or urban location were analyzed, changes in the electric heating coefficient suggested that we could not separate the effects of location and electric heating. However, this was not true for the effects of outdoor UFPs and electric heating as no major changes in model coefficients were observed when

separate models were analyzed for these two variables. Therefore, this suggested that we could separate the individual contributions of electric heating and outdoor UFPs to indoor UFP exposures. Other correlated variables did not result in marked changes in coefficients when separate models were analyzed, and thus the remaining variables were explored in multivariable models.

Multivariable Models for Mean UFP Exposures

In multivariable models, electric oven use (β=12,253, 95% CI: 3524, 20,982), indoor relative humidity (β=1136, 95% CI: 372, 1899) and indoor smoking (β=18,192, 95% CI: 2073, 34,311) were each significant determinants of mean indoor UFP exposures (Table 4). Comparable results were obtained in a simplified multivariate model which classified home heating system type as either enclosed or exposed, but having an enclosed type of heating system was not associated with lower mean UFP exposures (β=1843, 95% CI: -9152, 12,839).

Multivariable Models for Overnight Baseline UFP Exposures

In a multivariable model exploring determinants of overnight baseline UFP exposures, air exchange rate (β= 4351, 95% CI: 1507, 7195) and each 10,000 cm^{-3} increase in outdoor UFPs (β=811, 95% CI: 244, 1377) were identified as significant determinants (Table 5). Similar results were observed in a multivariable model considering home heating system type as either enclosed or exposed, with overnight baseline exposures being significantly lower in homes with enclosed types of heating systems (β= -1710, 95% CI: -3330, -91). The tendency for homes with enclosed types of heating systems to have lower overnight baseline UFP exposures is depicted for non-smoking homes in Figure 5.

Real-Time Comparison of Overnight UFPs

Although home heating systems were not identified as significant determinants of mean or baseline UFP exposures in multivariable models, we observed evidence indicating that home heating systems are nevertheless a source of indoor UFPs. In Figure 6, real-time measures of indoor UFPs and temperature (as a sign of heating system activation) are shown during overnight hours in four homes. A clear pattern of decreasing indoor UFPs with decreasing temperature was observed in a home with a stand-alone wood stove (Figure 6a). Although this may be owing to the extinguishing of the fire over the course of the night, we cannot rule out a simultaneous decline in outdoor UFPs as the primary cause of this relationship because outdoor measures were not collected during this time period. In a home using electric baseboard heaters, indoor UFP concentrations were observed to increase and decrease with temperature, with UFP peaks occurring at temperature minimums (Figure 6b). Although we did not investigate the specific source of these particles on electric heaters, dust seems unlikely as UFP peaks did not decrease throughout the night as would be expected if the burning of accumulated dust was the principle source. Regardless, similar patterns were observed in homes with forced-air oil (Figure 6c) and natural gas furnaces (Figure 6d), suggesting that these types of systems also contribute to indoor UFPs.

Correlation between Measured and Predicted UFP Exposures in Homes

A predictive model developed using a sub-set of home data is shown in Table 6, and a summary of observed and predicted values for UFP exposures in homes is presented in Table 7. For comparison, a predictive model developed using data from all homes combined is presented in Table 8, and is generally consistent with the model developed using a sub-set of homes with the exception of an additional term for home volume.

On average, model predictions for UFP exposures in homes underestimated observed values by 944 cm^{-3} (95% CI: -9247, 11,136). While this difference was rather small, only a modest correlation was detected between observed and predicted UFP levels in homes ($r = 0.28$). The strength of this relationship improved with the removal of three outlying data points which exceeded a difference of 10,000 cm^{-3} ($r = 0.54$) (Figure 7). In general, however, model performance was poor and further evaluation is required to judge the merit of similar models.

Discussion

In a cross-sectional survey of indoor UFP exposures, home heating system type was not identified as a significant determinant of mean or baseline UFP exposure in multivariate models. However, homes with enclosed types of heating systems did have significantly lower baseline exposure levels after adjusting for a number of potential confounding factors including outdoor UFPs. We are unaware of other investigations examining in-home UFP exposures according to the type of heating system, but one limitation of this study was our inability to detect UFPs smaller than 20 nm. As a result, it is possible that indoor UFP exposures were underestimated in natural gas heated homes as the combustion of natural gas is known to produce UFPs below this size limit (Wallace, 2000). On the other hand, underestimation of exposures owing to gas cooking was not an issue because all homes used electricity for cooking. Furthermore, it should be stated that the Dust Trak employed in this investigation does not provide ideal measures of particulate matter exposures, and may overestimate exposures determined by reference gravimetric methods (Jenkins et al., 2004).

The identification of electric oven use and cigarette smoking as significant predictors of mean indoor UFP exposures in this study is consistent with previous studies which have shown these to be strong sources of indoor UFPs (Dennekamp et al., 2001; Afshari et al., 2005). Likewise, the observed pattern of increased indoor UFPs during the evening relative to overnight hours has also been reported previously (Abt et al., 2000; Wallace and Howard-Reed, 2002), and supports the role of cooking as an important source of indoor UFPs. Furthermore, our finding of indoor relative humidity as a significant predictor of mean indoor UFP exposures is consistent with the fact that UFP growth depends in part on the availability of condensable vapors which participate in gas to particle conversions (Kulmalaet al., 2004).

Outdoor UFPs were important determinants of overnight baseline UFP exposures in the homes examined, and this is consistent with previous findings suggesting that outdoor UFPs are significant predictors of indoor levels in the absence of strong indoor sources (Levy et al., 2002; Matson, 2005). In addition, this finding draws attention to the fact that home heating systems were not strong contributors to indoor UFPs in this study. However, it should be stated that indoor UFP concentrations cannot be directly estimated from outdoor measures when strong indoor sources are present (Wallace and Howard-Reed, 2002; Hussein et al., 2005). Nevertheless, outdoor UFPs can influence indoor levels and this relationship likely depends in part on home ventilation. Indeed, air exchange rates were significant determinants of overnight baseline UFP exposures in this study, and previous reports suggest that air exchange rates may have a significant impact on indoor particle levels (Abtet al., 2000; Asmi et al., 2004). In homes, simply opening windows can have a dramatic effect on air exchange rates (Wallace et al., 2002); however, this relationship was not addressed in the current study as windows were generally kept closed in participant homes.

We have recently addressed the need for further research into the potential respiratory effects of indoor UFP exposures (Weichenthal et al., 2007a), and we suspect that increased indoor UFP concentrations may contribute to previously reported associations between electric baseboard heaters and childhood asthma (Infante-Rivard, 1993; Findley et al., 2003). Indeed, this study and others (Afshari et al., 2005) have identified electric baseboard heaters as a source of indoor UFPs. Stand-alone wood stoves also appeared to be a source of indoor UFPs in this study, and the composition of these particles may be particularly important because wood smoke is known to contain respiratory irritants such as formaldehyde, nitrogen oxides, and sulfur dioxide (Larson and Koenig, 1994). To determine the relative toxicities of UFPs produced by different

indoor sources, further research is needed into their respective chemical compositions. Indeed, without this knowledge, it remains difficult to raise alarm about UFPs produced by home heating systems when cooking and smoking are much stronger sources. A recent study has made progress in the area of indoor particle composition (See and Balasubramanian, 2006), and suggests that aerosols produced during gas cooking may contain toxic metals. However, this study examined exposures in a commercial kitchen and may not adequately reflect in-home UFP exposures. Nevertheless, low-level indoor UFP sources such as home heating systems may have important public health implications if cumulative rather than peak indoor UFP exposures are found to be associated with respiratory disorders. As such, separating the independent health effects of indoor UFPs and larger-sized particles is likely to remain a challenge as our findings and others (Levy et al., 2002) suggest that these types of exposures tend to be correlated.

Using a model developed from a sub-set of participants we observed a modest correlation between observed and predicted UFP levels in homes. Other investigations attempting to model in-home UFP levels were not identified, but our findings suggest that modeling short-term indoor UFP levels may be difficult owing to the transient nature of indoor UFP emissions. However, further evaluation is required as the model developed in this study and/or similar models may provide better estimates of weekly or monthly-average indoor UFP exposures than short-term exposures over a single day.

Conclusions

Home heating systems do not appear to be significant determinants of mean or baseline indoor UFP exposures, and sources such as cooking and smoking are likely much more important predictors of in-home UFP levels. Nevertheless, real-time measures suggest that home heating systems do contribute to indoor UFP levels, and further investigation is warranted, particularly for the smaller particle size fractions (< 20 nm) not examined in this study. While only a modest correlation was observed between measured and predicted indoor UFP levels, further evaluation is required as similar models may be useful in large-scale investigations interested in the potential health effects of UFP exposures. In the future, it will also be important to understand the chemical composition of UFPs produced indoors if we are to fully appreciate their potential impact on public health.

Acknowledgements

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TABLES

Table 1. Home characteristics[a]

Home Characteristic	Type of Primary Home Heating System			
	Electric Baseboard Heaters	Wood Stove	Forced-Air Oil Furnace	Forced-Air Gas Furnace
	n=9	n=7	n=10	n=10
	Mean (SD[b])	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	71.5 (30)	26.7 (17)	40.3 (26)	47.4 (26)
Volume (m^3)	511.5 (449)	1198 (398)	686.8 (343)	1114 (179)
Number of Occupants	1.7 (0.86)	2.4 (1.4)	2.6 (0.7)	3.0 (1.2)
Number of Smokers	4 homes contained 1 smoker	3 homes contained 1 smoker	1 home contained 1 smoker	No smokers
Number of homes in an urban location	6	1	1	0

[a] All homes used electricity for cooking; [b] Standard deviation.

Table 2. Summary of in-home measures and outdoor UFPs

Parameter Measured	Type of Primary Home Heating System							
	Electric Baseboard Heaters		Wood Stove		Forced-Air Oil Furnace		Forced-Air Gas Furnace [a]	
	n=9		n=7		n=10		n=10	
	Mean (SD[b])	(95% CI [c])	Mean (SD)	(95% CI)	Mean (SD)	(95% CI)	Mean (SD)	(95% CI)
Outdoor UFP [d]	29,558 (20,852)	(13,350, 45,587)	15,372 (12,499)	(3813, 26,932)	10,634 (8061)	(4867, 16,401)	14,491 (12,209)	(5757, 23,225)
Indoor UFP [e]	17,064 (15,999)	(4765, 29,362)	17,546 (12,092)	(6362, 28,730)	11,039 (8910)	(4664, 17,413)	13,009 (15,121)	(2192, 23,827)
Baseline UFP [f]	5048 (3833)	(2101, 7994)	2412 (1635)	(900, 3925)	1600 (1528)	(506, 2693)	943 (517)	(573, 1313)
PM_4 [g]	69.4 (98)	(0, 144)	62.5 (64)	(0, 122)	35.3 (40)	(4, 66)	21.5 (22)	(5, 37)
Ach [h]	0.46 (0.35)	(0.19, 0.73)	0.31(0.04)	(0.07, 0.50)	0.26 (0.15)	(0.15, 0.37)	0.32 (0.22)	(0.16, 0.47)
RH (%)[i]	24.4 (4)	(21, 28)	31.5 (4)	(27, 35)	27.0 (6)	(22, 32)	30.0 (8)	(24, 36)
Indoor Temperature (°C)	20.7 (2)	(19, 22)	22.3 (4)	(19, 26)	22 (1)	(21, 23)	19.8 (2)	(18, 22)

[a] Nitrogen dioxide was not detected (<0.01ppm) in any home. [b] Standard deviation; [c] 95% Confidence interval; [d] 10-second average ultrafine particle number concentration (cm^{-3}) outside each group of homes prior to indoor sampling (approximately 1600-1700); [e] Indoor ultrafine particle exposure (cm^{-3}); [f] Overnight baseline indoor ultrafine particle exposure (cm^{-3}); [g] Mass concentration of respirable particulate matter less than 4.0μm in diameter ($\mu g/m^3$); [h] Air exchange rate (h^{-1}); [i] Indoor relative humidity.

Table 3. Spearman's correlation coefficients for independent variables

	Electric heating	Wood heating	Gas heating	Oil heating	Outdoor UFP	Ach	Temp	Home age	Home volume	RH	Oven used	Indoor smoking	Location
Outdoor UFP	0.33	0.0	-0.07	-0.25	1								
Ach[a]	0.20	-0.11	0.14	-0.25	0.10	1							
Temp[b]	-0.12	0.21	-0.30	0.25	-0.15	-0.39*	1						
Home age	0.40*	-0.35*	0.02	-0.10	0.30	0.16	-0.29	1					
Home volume	-0.48*	0.31	0.41*	-0.23	-0.48*	-0.16	-0.03	-0.49*	1				
RH[c]	-0.32	0.30	0.13	-0.09	-0.04	-0.08	-0.17	-0.08	0.39*	1			
Oven used	-0.06	0.04	0.01	0.01	0.02	-0.17	0.29	-0.28	0.09	0.27	1		
Indoor smoking	0.32	0.21	-0.25	-0.25	-0.16	-0.02	0.17	0.03	0.20	-0.06	0.0	1	
Urban Location	0.62*	-0.10	-0.33*	-0.18	0.54*	0.23	-0.29	0.49*	-0.52*	-0.33	-0.15	-0.02	1

[a]Air exchange rate (h^{-1}); [b] Indoor temperature; [c] Indoor relative humidity;*Correlation significant at 0.05 level.

Table 4. *Multivariable model for determinants of mean indoor UFP exposure*

Dependent Variable	Independent Variables	β	95% CI [a]
Mean indoor UFP exposure (cm^{-3})	Oil furnace heating	Reference heating system[b]	
	Electric baseboard heating	5278	(-10,391, 20,948)
	Wood stove heating	-1431	(-16,084, 13,221)
	Natural gas furnace heating	5109	(-8769, 18,987)
	10 year increase in home age	109	(-1804, 2023)
	Increase of 10,000 cm^{-3} in outdoor UFP concentration	1561	(-2108, 5231)
	Increase of 500 m^3 in home volume	-1805	(-10,423, 6811)
	Air exchange rate (h^{-1})	7650	(-10,763, 26,064)
	Mean indoor temperature (°C)	1709	(-454, 3872)
	Mean indoor relative humidity (%)*	1136	(372, 1899)
	Electric oven used*	12,253	(3524, 20,982)
	Indoor cigarette smoking*	18,192	(2073, 34,311)

[a] 95% Confidence interval; [b] Coefficients for other heating systems are in reference to oil heating homes; * Statistical significance (95% CI excludes the null).

Table 5. Multivariable model for determinants of overnight baseline UFP exposure

Dependent Variable	Independent Variables	β	95% CI [a]
Overnight baseline indoor UFP exposure (cm^{-3})	Oil furnace heating	Reference heating system[b]	
	Electric baseboard heating	612	(-1807, 3032)
	Wood stove heating	1128	(-1134, 3391)
	Natural gas furnace heating	-579	(-2722, 1564)
	10 year increase in home age	82	(-214, 377)
	Increase of 10 000 cm^{-3} in outdoor UFP concentration*	811	(244, 1377)
	Increase of 500 m^3 in home volume	-295	(-1626, 1035)
	Air exchange rate (h^{-1})*	4351	(1507, 7195)
	Mean indoor temperature (^oC)	30	(-304, 364)
	Mean indoor relative humidity (%)	-102	(-220, 16)
	Electric oven used	172	(-1103, 1447)
	Indoor cigarette smoking	451	(-2039, 2940)

[a] 95% Confidence interval; [b] Coefficients for other heating systems are in reference to oil heating homes; * Statistical significance (95% CI excludes the null).

Table 6. Predictive model for mean UFP exposures in homes - developed using a sub-set of homes[a]

Dependent Variable	α	95% CI	Independent Variable	β	95% CI
Mean indoor UFP exposure (cm^{-3})	-6485	(-24,556, 11,586)	Mean indoor relative humidity (%)	488	(-143, 1119)
			Electric oven used	2900	(-5057, 10,856)
			Indoor cigarette smoking	18,080	(7423, 28,736)

[a] Model is for the mean UFP exposure over the evening and overnight periods combined and was developed using data from the first 26 homes sampled.

Table 7. Summary of observed and predicted UFP exposures in homes.

Observed UFP Exposure (cm^{-3})[a]			Predicted UFP Exposure (cm^{-3})[a]		Difference (cm^{-3})[b]	
N	Mean	95% CI	Mean	95% CI	Mean	95% CI
10	12 355	(2154, 22 556)	11 410	(7364, 15 457)	944	(-9247, 11 136)

[a] Mean UFP exposure in homes over the evening and overnight periods combined;

[b] Difference = Observed-Predicted

Table 8. Final predictive model for mean UFP exposures in homes[a]

Dependent Variable	α	95% CI	Independent Variable	β	95% CI
Mean UFP Exposure (cm^{-3})	-20 440	(-36,224,-4655)	Mean indoor relative humidity (%)	865.5	(275, 1460)
			Home volume (m^3)	-2.95	(-12, 5.8)
			Electric oven used	9757	(2836, 16,678)
			Indoor cigarette smoking	13,770	(3965, 23,574)

[a] Model is for the mean UFP exposure in homes over the evening and overnight periods combined and was developed using data from all homes.

FIGURES

Figure 1. Mean indoor UFP exposures during the evening and overnight hours. The shaded box spans the 25th and 75th percentiles. The upper and lower adjacent lines indicate maximum and minimum values respectively. The white lines indicate median values. Dots indicate outlying values.

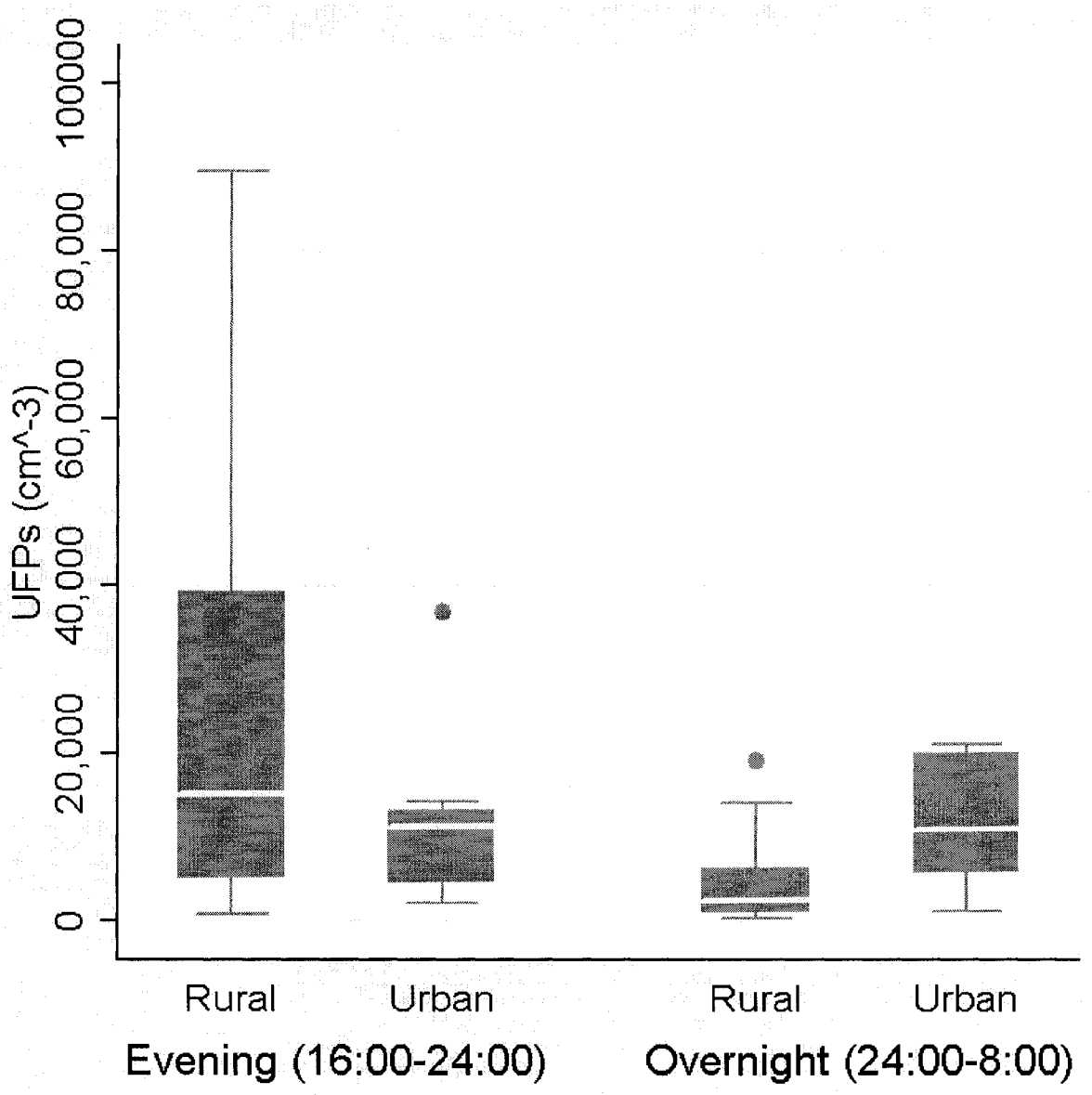


Figure 2. Mean (dark grey) and baseline (light grey) UFP exposures in homes with different heating systems. The shaded box spans the 25th and 75th percentiles. The upper and lower adjacent lines indicate maximum and minimum values respectively. The white lines indicate median values. Dots indicate outlying values.

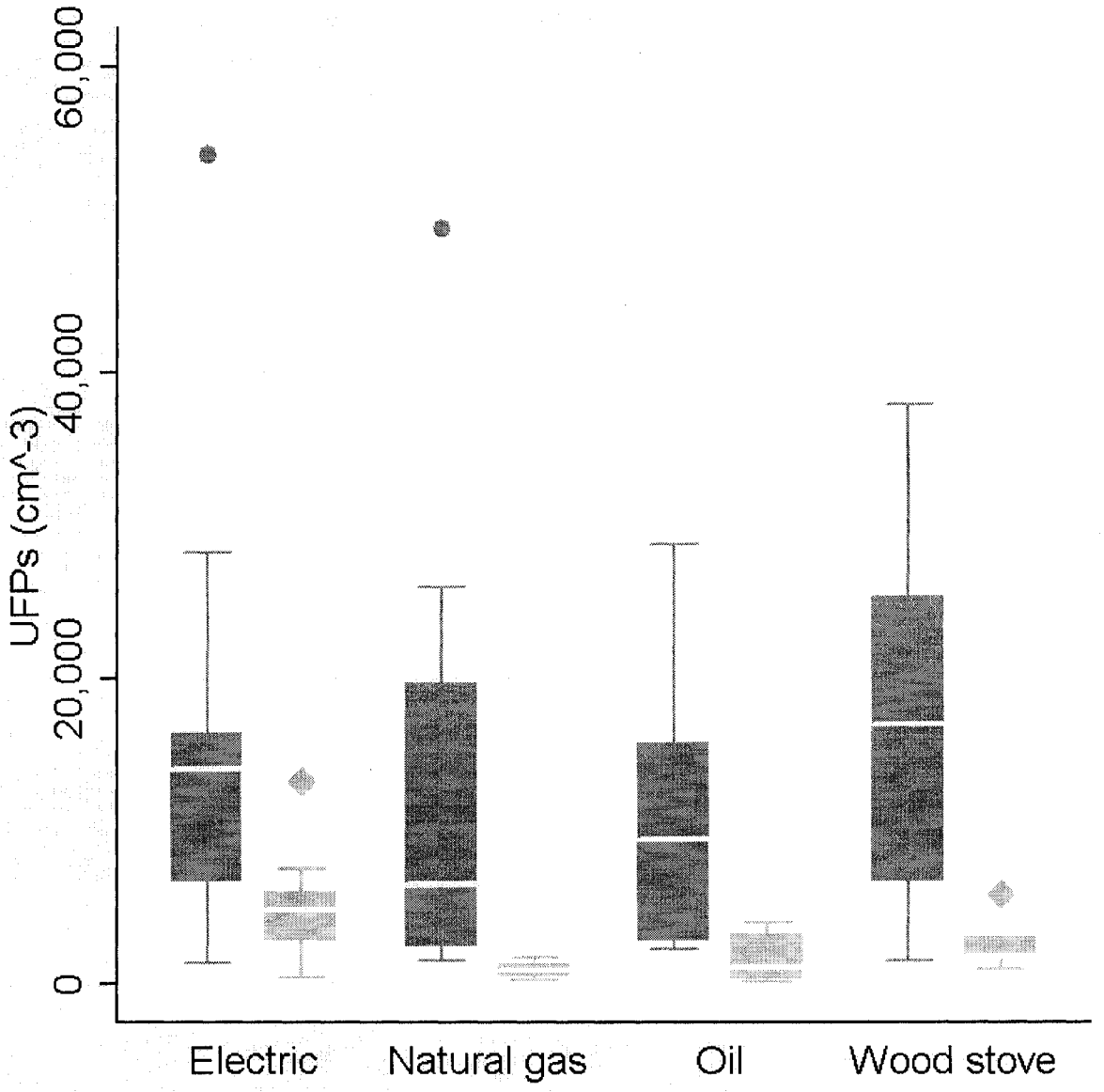


Figure 3. Scatter-plot of mean indoor UFP exposure (cm^{-3}) and mean indoor PM_4 exposure ($\mu g/m^3$). Shaded area indicates 95% confidence interval around line of best fit.

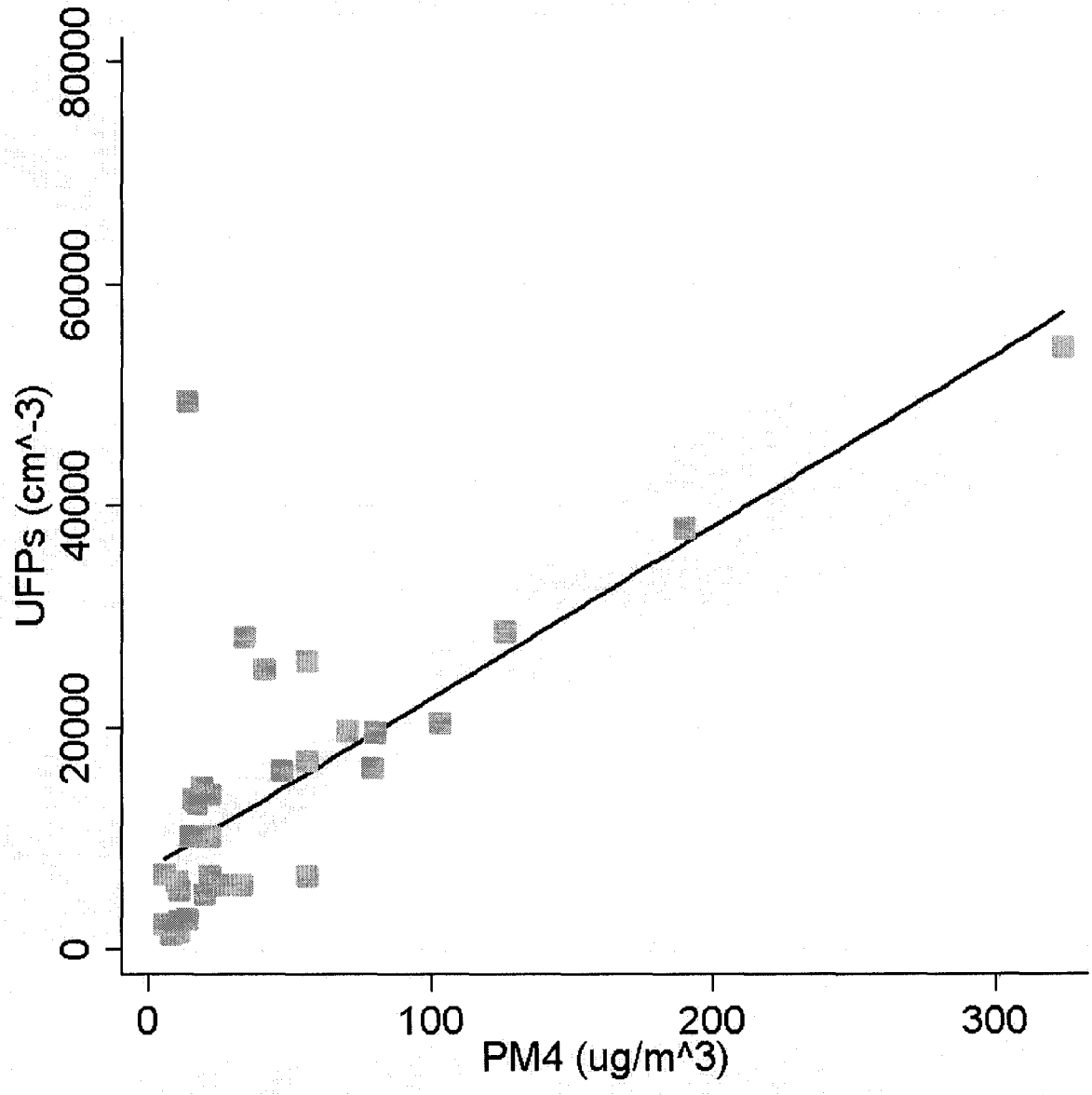


Figure 4a. Scatter-plot of overnight baseline UFP exposure (cm^{-3}) and outdoor UFPs (cm^{-3}). Shaded area indicates 95% confidence interval around line of best fit.

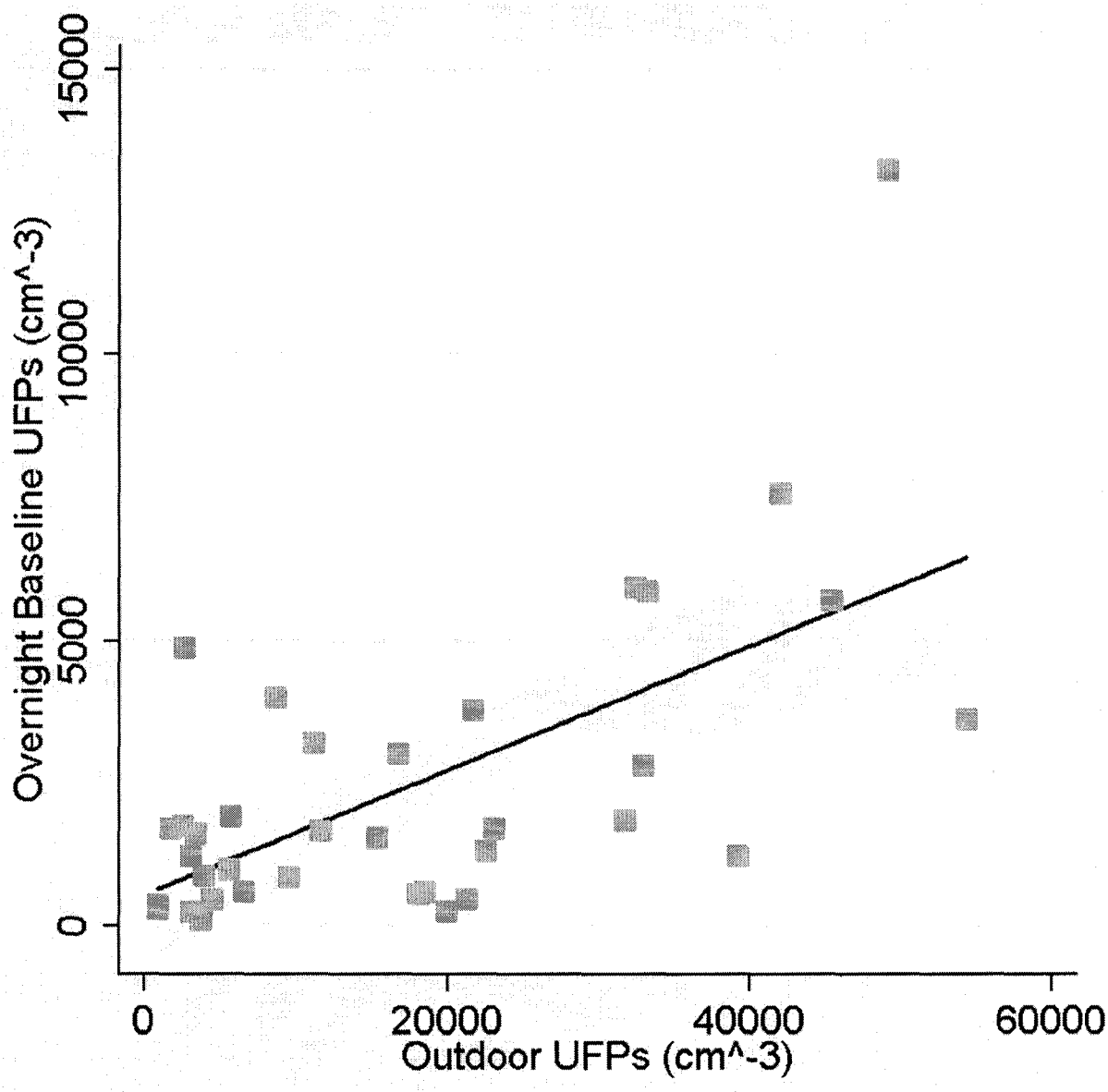


Figure 4b. Scatter-plot of overnight baseline UFP exposure (cm^{-3}) and air exchange rate. Shaded area indicates 95% confidence interval around line of best fit.

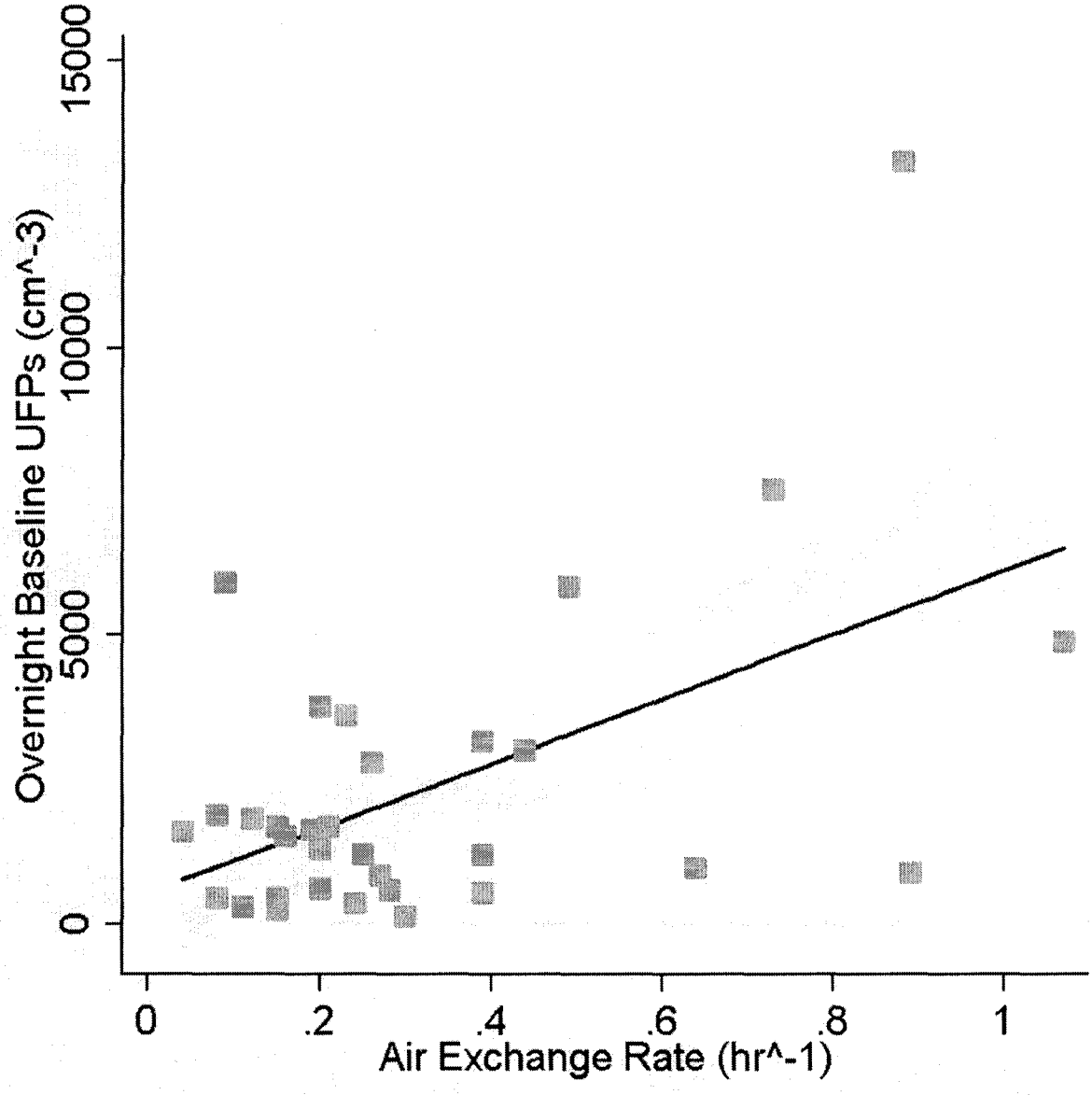


Figure 5. Overnight baseline UFP exposures (cm^{-3}) in non-smoking homes. Forced-air furnaces using oil, natural gas, or wood were classified as enclosed and electric baseboard heaters and stand-alone wood stoves were classified as exposed. The shaded box spans the 25th and 75th percentiles. The upper and lower adjacent lines indicate maximum and minimum values respectively. The white lines indicate median values. Dots indicate outlying values

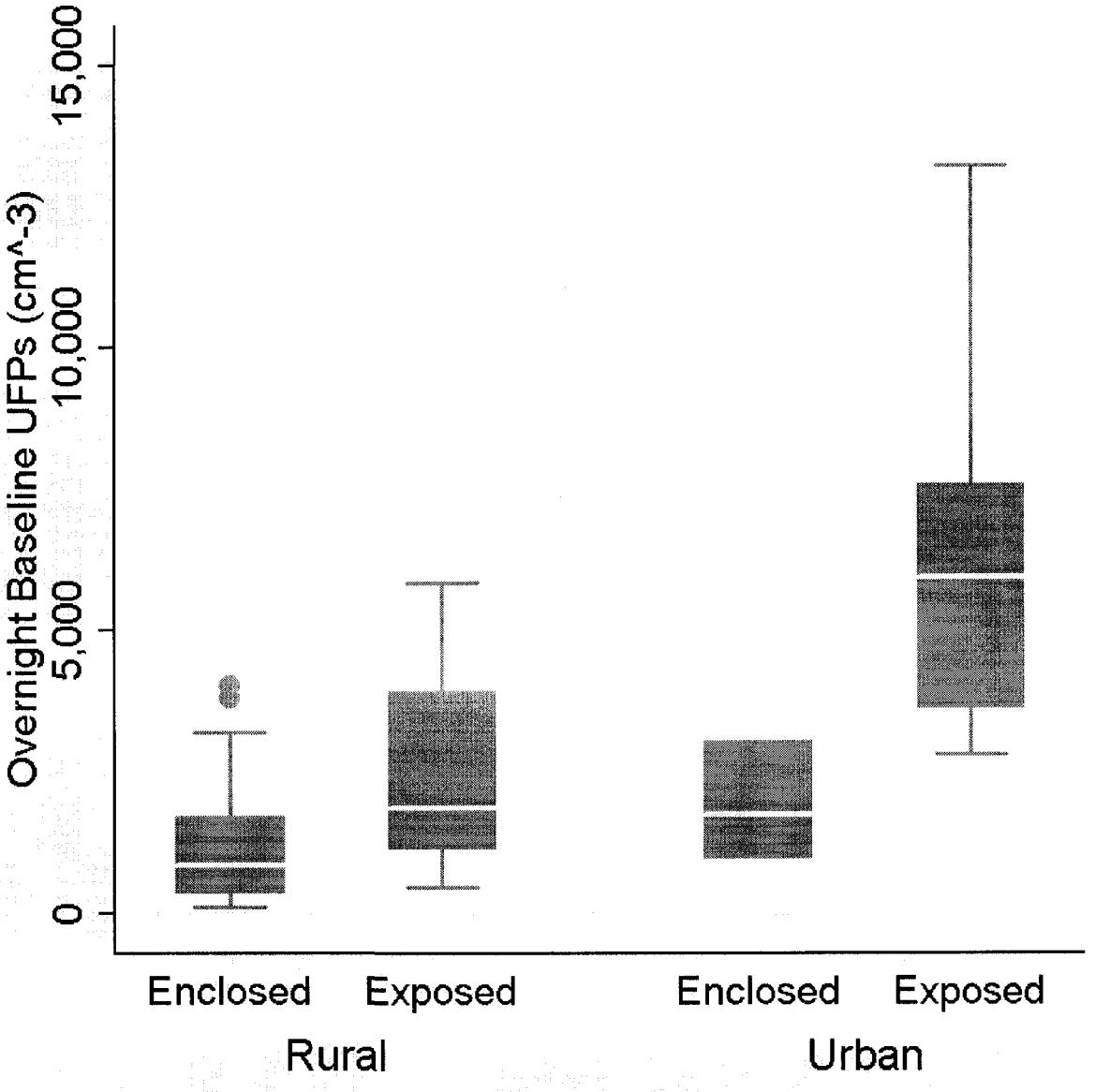


Figure 6a and 6b. Real-time overnight indoor UFP concentrations (cm^{-3}) (top line) and temperature (^{o}C) (bottom line) as a sign of home heating system activation. (A) Home with a stand-alone wood stove, (B) Home with electric baseboard heaters.

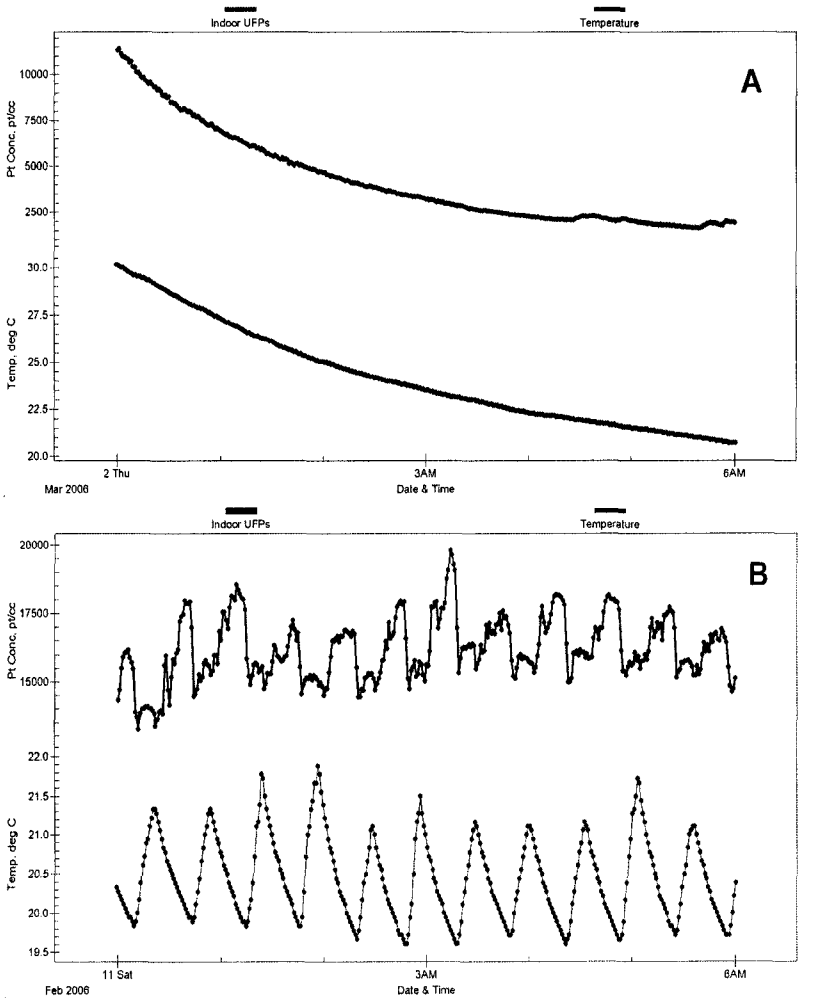


Figure 6c and 6d. Real-time overnight indoor UFP concentrations (cm^{-3}) (top line) and temperature (^{o}C) (bottom line) as a sign of home heating system activation. (C) Home with a forced-air natural gas furnace, (D) Home with a forced-air oil furnace.

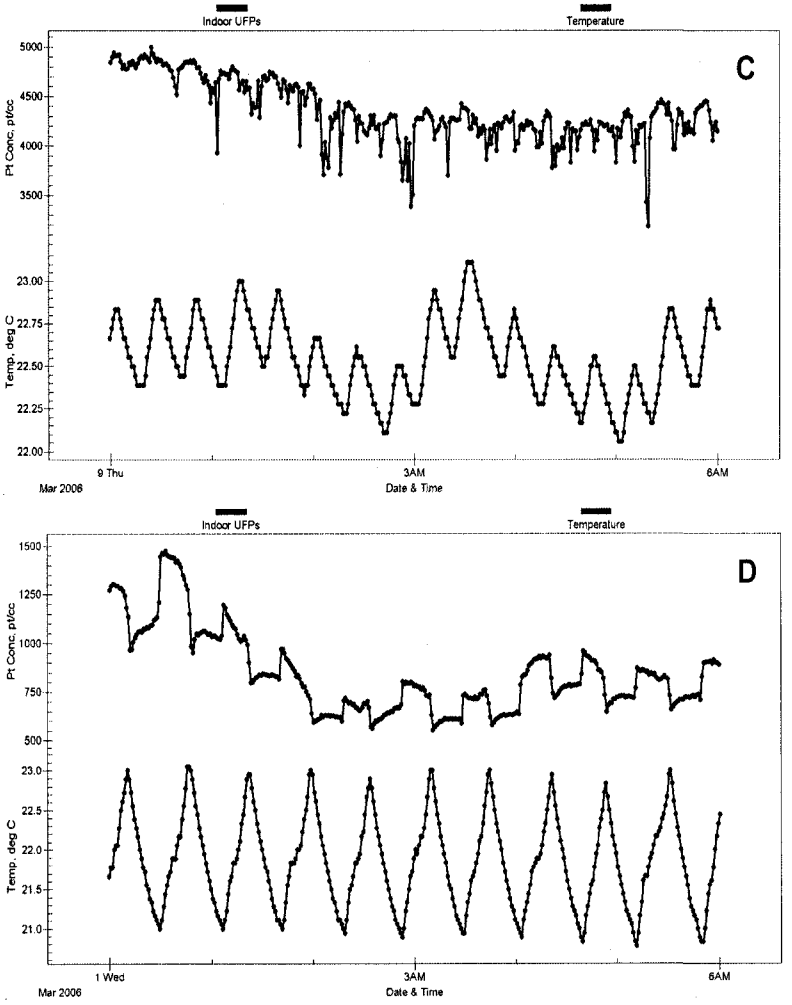
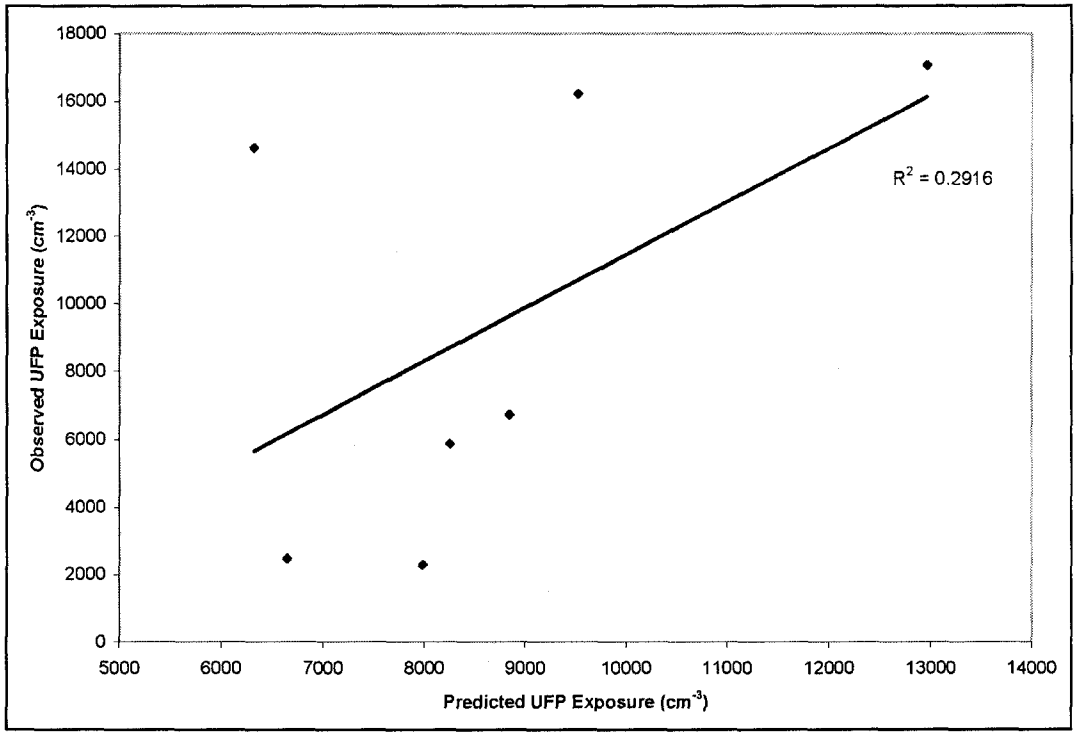


Figure 7. Correlation between measured and predicted UFP exposures in participant homes (three outliers removed).



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3.1 PREFACE TO MANUSCRIPT C

Between home and work or school, people often spend a considerable portion of their time in transportation environments including public transit buses, private automobiles, and urban sidewalks. As vehicle traffic is a primary source of ambient UFPs, exposures in these types of environments may have an important impact on personal UFP exposures. To date, only a small number of studies have examined UFP levels in transportation environments and none have attempted to model such exposures. These types of models are of interest, however, because they could be used to supplement home exposure data to arrive at more complete estimates of participant UFP exposures in population-based studies. To address these issues, we conducted an investigation to explore determinants of UFP exposures in transportation environments and developed models to predict such exposures based on window opening behavior and ambient weather conditions. The following manuscript describes the findings of this study.

4. MANUSCRIPT C

DETERMINANTS OF ULTRAFINE PARTICLE EXPOSURES IN TRANSPORTATION ENVIRONMENTS: FINDINGS OF AN 8-MONTH SURVEY CONDUCTED IN MONTRÉAL, CANADA

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Running Title: Ultrafine particles and transportation environments

Key words: Ultrafine particles, personal exposures, transportation environments, exposure modeling.

Abstract

An 8-month sampling campaign was conducted in Montréal, Canada to explore determinants of ultrafine particle (UFP) exposures in transportation environments and to develop models to predict such exposures. Between April and November 2006, UFP (0.02-1μm) count exposure data was collected for one researcher during 80 morning and evening commutes including a 0.5 km walk, a 3 km bus ride, and a 26 km automobile ride in each direction. Ambient temperature, relative humidity, precipitation, and wind speed/direction data were collected for each transit period and the positions of bus and automobile windows were recorded. Mixing heights were also estimated. Morning UFP exposures were significantly greater than those in the evening, with the highest levels observed in the automobile and the lowest while walking. Wind speed and mixing height were highly correlated, and as a result only wind speed was considered in multivariable models owing to the accessibility of quantitative hourly monitoring data. In these models, each 10°C increase in morning temperature was associated with decreases of 14,560 cm^{-3} (95% CI: 11,111, 18,020), 8160 cm^{-3} (95% CI: 5060, 11,260), and 11,310 cm^{-3} (95% CI: 6820, 15,810) for UFP exposures in walk, bus, and automobile environments respectively. Likewise, each 10 km/h increase in morning wind speed corresponded to decreases of 8252 cm^{-3} (95% CI: 5130, 11,360), 6210 cm^{-3} (95% CI: 3420, 9000), and 6350 cm^{-3} (95% CI: 2440, 10,260) for UFP exposures in walk, bus, and automobile environments respectively. Similar trends were observed in the evening hours. In an evaluation of model performance, moderate correlations were observed between measured and predicted UFP exposures on new bus ($r = 0.65$) and automobile ($r = 0.77$)

routes. Further research is required to incorporate variables such as traffic density and vehicle ventilation settings into the models presented.

Introduction

Ultrafine particles (<0.1μm) (UFPs) are potent triggers of oxidative stress and inflammation in the lungs (Oberdörster et al., 1994; Li et al., 1996; Afaq et al., 1998; Zheng et al., 1998; Brown et al., 2001; Dick et al., 2003; Li et al., 2003; Gilmour et al., 2004), and are of interest in transportation environments because they are formed from vehicle exhaust (Cyrys et al., 2003; Gidhagen et al., 2004; Geller et al., 2006). Indeed, ambient UFP exposures may promote symptoms such as wheezing, cough, and shortness of breath among adult asthmatics (Von Klot et al., 2002), and some evidence suggests that the respiratory effects of UFPs are as strong or stronger than those of larger fine ($PM_{2.5}$) or course (PM_{10}) particles (Peters et al., 1997; Penttinen et al., 2001a; Penttinen et al., 2001b). In addition, UFP exposures may trigger adverse cardiovascular outcomes (Delfino et al., 2005) and contribute to cardiovascular mortality among susceptible individuals (Wichmann et al., 2000; Stölzel et al., 2006). Specifically, increases in ambient UFP counts of approximately 10,000 cm^{-3} have been associated with increases in daily mortality of 3% (Stölzel et al., 2006) and 4.5% (Wichmann et al., 2000) respectively with a lag of 4 days. Similar increases in personal UFP exposures have also been associated with decreased heart rate variability among subjects with impaired lung function (Chan et al., 2004). Indeed, the impact of UFP exposures may be most troubling for individuals suffering from asthma or obstructive pulmonary diseases as pulmonary deposition is greatest for these individuals (Brown et al., 2002; Chalupa et al., 2004; Frampton et al., 2004). However, UFP exposures are also a concern for healthy subjects as recent findings suggest that traffic-related UFP exposures may lead to oxidative DNA damage (Vinzents et al., 2005). Therefore, there is currently a need to characterize UFP

exposures in transportation environments because people spend a considerable portion of their day in these locations and evidence to date suggests that such exposures may have an adverse effect on respiratory and cardiovascular health. In addition, exposure assessment models are required for UFPs if we hope to further explore their potential health effects in population-based studies (Sioutas et al., 2005).

In England, pedestrian UFP exposures were examined for 12-days over a 500 meter stretch of roadway in Central London, and in this study UFP levels were significantly greater when walking curbside as compared to when walking near buildings (Kaur et al., 2005a). This finding is consistent with those of a more recent investigation which suggest that pedestrian UFP exposures are largely influenced by proximity to pollutant sources (Kaur et al., 2006). In Boston, Massachusetts, UFP levels were examined on buses and subways for several days during the summer months but no marked differences were observed with respect to outdoor concentrations (Levy et al., 2002). However, UFP levels in this study tended to be greater in buses than in subways (Levy et al., 2002). A second study conducted in London, England, over a 4-week period reported higher UFP levels in buses and automobiles as compared to cycling and walking (Kaur et al., 2005b), and a similar pattern was observed in a Health Canada study which reported UFP levels during walking to be approximately one-third of those measured in school buses (Health Canada, 2005).

Here we present findings of an 8-month sampling campaign designed to explore determinants of UFP exposures in transportation environments. In doing so, we describe exposures on a single transit route during morning and evening commutes over three seasons (spring, summer, autumn). Three transportation environments are considered

(walking, bus, automobile), and for each environment/time-period we estimate the effects of ambient temperature, relative humidity, mixing height, precipitation, and wind speed/direction on UFP exposures as well as window opening for buses and automobiles. Finally, we evaluate the correlation between measured and predicted UFP exposures on new bus and automobile routes.

Methods

Transit route

Personal UFP exposure data was collected three weekdays per week between April and November 2006 for one researcher during morning (7am-8am) and evening (4pm-5pm) commutes over a 29.5 km transit route in Montréal, Canada. This route was traversed in three sections including a 0.5 km walk, a 3 km ride in a diesel-fueled public transit bus, and a 26 km ride in a gasoline-fueled automobile (Mazda 3, 2006) in each direction. Quantitative traffic count data was not available from the city of Montréal for the walk and bus routes included in this study. However, traffic counts were estimated to be approximately 500 vehicles per hour for the walking route and 2000 vehicles per hour for the bus route using video data collected on a typical transit day. The automobile route took place primarily along a major highway which Transport Québec lists as servicing more than 40,000 vehicles per day. Passenger vehicles were the predominant vehicle type along the walk and bus routes, whereas large diesel transport vehicles were frequently present along the automobile route.

Walking

The morning walking route covered equal distances of a busy 2-lane roadway leading to downtown Montréal and a quiet roadway which primarily services residential traffic. During the morning hours, the walking route began at a private residence and ended at a bus stop on the corner of a busy 3-lane roadway. As such, morning walking exposures included the time period spent waiting for the bus each morning. The evening walking route followed the same path as in the morning hours.

Public transit bus

The morning bus traveled along a busy 3-lane roadway and made a total of 9 stops. The evening bus route was slightly longer due to 3 additional stops, but also traveled along a busy 3-lane roadway. It was not possible to sample in the same location in each bus without inconveniencing other passengers, and as a result in-bus UFP exposures were monitored wherever space was available in the bus at the time of boarding.

Automobile

The morning automobile route took place primarily along a 20 km section of highway between Montréal and Pointe-Claire, Québec. The evening automobile route followed the same path as the morning, but ended just south of the morning starting point. All UFP exposure measures were collected in the front passenger seat of the automobile, and the driver was given no specific instructions and was simply asked to drive to and from work as normal. Ventilation and heating conditions were set by the driver to suit passenger comfort as would normally be the case in a passenger vehicle.

Transit route for model evaluation

To evaluate model performance, personal UFP exposure data was collected for an additional 24 days between December, 2006 and March, 2007 on new bus and automobile routes. Using video data, traffic counts on the new bus route were estimated to be approximately 1000 vehicles per hour. This route took place primarily along a busy 2-lane roadway with the exception of a short stretch of quiet single-lane residential roadway on the evening route. Morning and evening bus routes were each approximately

3 km in length, with morning and evening routes located approximately 0.3 km and 0.6 km east of the route used for model development respectively.

Automobile measurements were collected in the morning only, and the route took place primarily along a second major highway between Montréal and Pointe-Claire, Québec. The main portion of the automobile route was approximately 7 km north of the original route used for model development, and according to Transport Québec also services more than 40,000 vehicles per day. Model performance was not evaluated on a different walking route because outdoor temperatures between December, 2006 and March, 2007 were generally below the minimum recommended operating temperature for the P-TRAK (below $0^{o}C$).

Data collection

Ultrafine particles

Ultrafine particle counts (cm^{-3}) were collected at 10-second sampling intervals in each transportation environment using a TSI P-TRAK Ultrafine Particle Counter (TSI Inc). This is a condensation particle counter with continuous data-logging capabilities and is capable of detecting particles between 0.02-1μm. The instrument was calibrated by the manufacturer prior to collecting field measurements, and exposure measures reflect time-weighted average UFP number concentrations in each transportation environment. The P-TRAK was equipped with a sampling wand and was carried at waist level in a shoulder bag with the sampling wand exposed to the external environment at all times. In each transportation environment the display screen of the P-TRAK remained visible to the researcher as to verify proper instrument function as well as to note potential causes (i.e. local sources) of abrupt changes in UFP concentrations. The P-TRAK was zero checked

and equipped with a newly recharged alcohol wick prior to each sampling period. For analysis, average UFP counts were determined over each transit period (i.e. morning and evening) and regressed against meteorological data averaged over the same time-period.

Weather data and window position

Time-specific ambient weather data was obtained from Environment Canada for each morning and evening transit period, and all temperature, relative humidity, and wind speed/direction values reflect measurements collected at Montréal's Trudeau International Airport. Precipitation was noted during each transit period, and bus and automobile windows were classified as open if at least one window was visibly ajar.

Mixing height is generally defined as the height of the atmospheric layer in which vigorous mixing takes place due to thermal and mechanical turbulence, with lower mixing heights favoring increased pollutant concentrations. However, unlike values for ambient temperature, relative humidity, and wind speed/direction, hourly mixing height data is not readily available for Montréal, Québec. As a result, mixing height values were estimated in this study according to the following equation (Cheng et al., 2001):

$$H_m = [121 \times (6-P) \times (T-T_d)/6] + [(0.169 \times P) \times (U_z + 0.257)/(12 \times f \times \ln(Z/Z_o)] \quad (1)$$

In this equation, H_m is the estimated mixing height (m), $T-T_d$ is the difference between ambient and dew point temperatures, U_z is wind speed (m/s) measured at the height Z (Z=10 m), Z_o is the surface roughness ($Z_o = 2.0$ m for urban areas), f is a constant accounting for the spin rate of the earth and the geographical latitude of Montréal, Québec, and P is the Pasquill stability class determined by wind speed and cloud cover during each transit period. In this study, P was generally equal to either 3 or 4 reflecting neutral or slightly unstable atmospheric conditions. A neutral atmosphere neither

enhances nor inhibits mixing in the atmosphere, whereas a slightly turbulent atmosphere promotes mixing. Previous findings suggest a relative error of approximately thirty percent for estimates obtained using the above model (Cheng et al., 2001), and while it is not the most accurate or complex model, it was the only model identified which could be readily applied given the meteorological data available.

Statistical analysis

All means, mean differences, standard deviations, 95% confidence intervals, box-plots, R^2-values, and scatter-plots were generated using the statistical software package STATA version 9.1 (Statacorp, College Station, TX, USA). Real-time plots of UFPs were produced using Trak Pro software available from TSI (TSI Inc., Shoreview, MN, USA), and scatter-plots of measured and predicted UFP exposures were generated using Microsoft Excel. The effects of each variable on UFP exposures in transportation environments were first explored in simple linear models and Spearman's correlation coefficients (r_s) were calculated to assess potential co-linearity between independent variables. If a substantial correlation was detected ($|r_s|>0.2$), three separate models were run (two models with each independent variable separately and one model with both variables present) and changes in model coefficients were noted. If no important changes in model coefficients were observed, the effects of both variables were explored. In all models, temperature (K), wind speed (km/h), mixing height (m), and relative humidity (%) were treated as continuous variables whereas precipitation, window position, and wind direction were treated as categorical variables. Wind direction was categorized as north, south, east, west, north-east, north-west, south-east, or south-west for each transit period and window position was recorded simply as open or closed.

Final model selection was performed using data from all time periods combined, and a dichotomous time-period variable (morning/evening) was also explored in final models. Interaction between independent variables was assessed in final models through the inclusion of first order interaction terms generated using centered variables in order to reduce correlations between interaction terms and independent variables. In selecting a final model, Bayesian Model Averaging (BMA) was employed using the statistical software package R version 2.4.0. Bayesian model averaging is advantageous because final model variables reflect a weighted average of all possible models weighted by the probability that each model is correct, thus accounting for model uncertainty (Kass and Raftery, 1995; Wasserman, 2000). In addition, Bayesian model selection has been shown to out-perform stepwise methods of model selection in making future predictions (Wang et al., 2004). As such, predicted values for UFP counts on different bus and automobile routes were generated using final multivariable models selected by BMA. The correlations (r) between measured and predicted UFP exposures were then assessed in simple linear models and were calculated as the square root of the coefficient of determination (R^2).

Results

In total, personal UFP exposure measurements were collected in each transportation environment for 80 morning and 80 evening commutes. On average, morning commutes were approximately 5-minutes shorter than in the evening, and temperature and wind speed tended to be higher in the evening while relative humidity tended to be higher in the morning. In addition, estimated mixing heights were higher in the evening relative to the morning hours. Summary statistics for daily travel times and ambient weather conditions throughout the study period are shown in Tables 1 and 2.

Ultrafine particle exposures in transportation environments

Ultrafine particle count exposure data is summarized in Table 3, and box-plots for mean UFP exposures are shown in Figure 1. Along the walking route, UFP levels were observed to increase when moving from a quiet street onto a busier roadway (data not shown), and parked, idling school buses appeared to be strong local sources of UFPs when walking (Figure 2a). Automobile UFP levels also increased when driving from 2 or 3-lane roadways onto highways (data not shown), and coach passenger buses appeared to trigger dramatic increases in UFP levels in both public transit buses and in the automobile (Figure 2b and 2c). In general, UFP exposures were significantly greater in the morning relative to the evening hours, with morning counts exceeding evening levels by 9382 cm^{-3} (95% CI: 6149, 12,615), 5402 cm^{-3} (95% CI: 1734, 9071), and 6858 cm^{-3} (95% CI: 3555, 10,162) for the walk, bus, and automobile environments respectively. Exposures also differed between environments, with morning automobile counts exceeding morning bus and walking levels by 10,319 cm^{-3} (95% CI: 5933, 14,705) and 13,187 cm^{-3} (95% CI: 8258, 18,115) respectively. Morning bus exposures were on average 2867 cm^{-3} (95% CI:

-1439, 7175) greater than when walking. A similar pattern was observed in the evening hours with mean automobile exposures exceeding mean bus and walking levels by 8863 cm^{-3} (95% CI: 5213, 12,513) and 15,710 cm^{-3} (95% CI: 12,611, 18,810) respectively, and mean bus exposures exceeding walking levels by 6847 cm^{-3} (95% CI: 3857, 9839). For all time-periods combined, mean automobile exposures were 9591 cm^{-3} (95% CI: 6677, 12,504) and 14,449 cm^{-3} (95% CI: 11 419, 17,478) greater than bus and walking exposures respectively, while mean bus counts exceeded walking levels by 4858 cm^{-3} (95% CI: 2120, 7595).

Correlation between independent variables

Relative humidity was inversely correlated with temperature (r_s = -0.48, n=160) and when both variables were included in models for each transportation environment and time-period, coefficients for temperature remained constant while coefficients for relative humidity decreased substantially. In addition, we observed no independent association between relative humidity or precipitation and UFP exposures in any transportation environment or time-period ($0.001 < R^2 < 0.06$); therefore, the effects of relative humidity and precipitation were not explored in multi-variable models. Likewise, no important effect was observed for wind direction ($0.001 < R^2 < 0.04$), and when the effect of wind speed was assessed according to direction, coefficients were similar for all wind directions (data not shown). As such, the effects of wind direction were not explored in multivariable models.

Moderate inverse correlations were observed between morning time-period and temperature (r_s = -0.33, n=160) and wind speed (r_s = -0.31, n=160). A moderate correlation was also observed between wind speed and the temperature-wind speed

interaction term (r_s = 0.28, n=160). However, no marked changes in model coefficients where observed when simple linear models were compared to models with all three variables and thus both time-period and temperature-wind speed interactions were explored as potential determinants in final multivariable models.

Wind speed and mixing height were highly correlated (r_s = 0.97, n=160) and the independent effects of these two variables could not be separated in multivariable models. Given this result, wind speed alone was considered in final predictive models as quantitative monitoring data was readily available for this variable, whereas mixing height data was estimated and is generally more difficult to obtain. For completion, however, the effects of mixing height on UFP exposures were assessed for all transit periods combined, and after adjusting for time-period and temperature each 1000 m increase in mixing height was associated with decreases of 1316 cm^{-3} (95% CI: 714, 1919), 1553 cm^{-3} (95% CI: 927, 2179), and 1735 cm^{-3} (95% CI: 992, 2478) for UFP exposures in walk, bus, and automobile environments respectively.

In the morning hours, bus window opening was highly correlated with temperature (r_s = 0.70, n=80). When both variables were included in the same model, the coefficient for temperature remained constant while the coefficient for bus window opening changed substantially; thus suggesting that the effect of bus window opening could not be separated from the effect of temperature in the morning hours. The correlation between temperature and bus window opening was lower in the evening hours (r_s = 0.52, n=80) and when both variables were included in the same model no dramatic changes in model coefficients were observed; therefore while the effect of morning bus window opening was not explored in multivariable models the effect of evening bus

window opening was assessed. Temperature and car window opening were slightly correlated in the morning hours (r_s = 0.29, n=80), and while the coefficient for car window opening increased slightly when temperature was included in the model, this did not change the overall interpretation of the effect of car window opening in the morning hours and thus this variable was included in multivariable models. No other significant interactions were detected between independent variables.

Multivariable models

Multivariable models estimating the effects of temperature, wind speed, and window opening in each transportation environment are shown in Tables 4 and 5. Window opening was not a significant determinant of UFP exposures in buses or automobiles, and no consistent effect of window opening was observed. However, temperature was a significant determinant of mean UFP exposures in all three transportation environments during the morning hours, with each 10°C (equivalent to a 10 K increase) increase in temperature corresponding to decreases in mean UFP exposure of 14,560 cm^{-3} (95% CI: 11,111, 18,020), 8160 cm^{-3} (95% CI: 5060, 11,260), and 11,310 cm^{-3} (95% CI: 6820, 15,810) for the walk, bus, and automobile environments respectively. Wind speed was also a significant determinant of UFP exposures in the morning hours, with each 10 km/h increase in wind speed corresponding to decreases in mean UFP exposure of 8252 cm^{-3} (95% CI: 5130, 11,360), 6210 cm^{-3} (95% CI: 3420, 9000), and 6350 cm^{-3} (95% CI: 2440, 10,260) for the walk, bus, and automobile environments respectively. A similar pattern was observed in the evening hours, but the effect of wind speed was not statistically significant for evening walking exposures and the effect of temperature was not statistically significant for evening bus exposures.

Scatter-plots of temperature and wind speed against mean UFP exposures in each transportation environment are depicted in Figure 3 for both time-periods combined.

Correlation between measured and predicted UFP exposures on a different bus and automobile route

To evaluate model performance, UFP exposure data was collected for an additional 22 mornings on a different automobile route and 24 mornings and 18 evenings on a different bus route between December 2006 and March 2007. In general, model evaluation days were colder than those used for model development (Mean= -3.0°C, SD=8.9) and wind speeds were slightly greater (Mean= 17.8 km/h, SD=9.8). Final multivariable models used for predicting UFP exposures are shown in Table 6, and a summary of observed and predicted values for UFP exposures on the new bus and automobile routes are presented in Table 7. A moderate correlation was observed between measured and predicted automobile UFP exposures (r = 0.50), with model estimates on average underestimating measured values by 3540 cm^{-3} (95% CI: -7190, 14,271). This correlation increased (r=0.77) (Figure 4a) with the removal of two outlying values for which no clear cause was noted. The correlation between measured and predicted bus exposures was comparable to that observed for the automobile (r=0.55), with model estimates on average overestimating measured values by 6289 cm^{-3} (95% CI: -11,818, -761). This correlation improved (r= 0.65) (Figure 4b) with the removal of two outlying values, one of which was collected on a morning in which the public transit bus traveled directly behind a school bus; again highlighting the importance of these vehicles as local sources of UFPs. However, no clear cause was apparent for the second outlying data point.

Discussion

An 8-month sampling campaign was conducted in Montréal, Canada, to explore determinants of UFP exposures in transportation environments and to develop models to predict such exposures. Walking, bus, and automobile environments were considered, and while relative humidity, precipitation, wind direction, and window opening had no marked effect on UFP counts, temperature and wind speed were each significant determinants of UFP exposures in all three transportation environments. However, we cannot rule out a potentially important effect for mixing height as a high correlation between wind speed and mixing height meant that the independent effects of these two variables could not be estimated in multivariable models. Nevertheless, models including wind speed alone may be more suitable for use in population-based studies owing to the accessibility of historical wind speed data for many locations in comparison to the lack of such data for mixing heights. Regardless, future studies should aim to include more accurate measures of mixing height than those employed in the current investigation in order to conduct a more comprehensive analysis of the effects of mixing height on UFP exposures in transportation environments.

Our findings are limited in that we provide no information on the number-weighted size-distribution or chemical composition of UFPs in transportation environments. In addition, we could not detect particles smaller than approximately 0.02μm, and as a result our findings likely underestimate UFP exposures in transportation environments. Indeed, freshly emitted vehicle exhaust is known to contain particles below this size limit (Kittelson 1998; Harrison et al., 1999; Zhu et al., 2002; Kittelson et al., 2004; Matson et al., 2004), and a recent study found that P-TRAK measures near a

busy motorway were consistently lower than those measured with a more sensitive instrument (Zhu et al., 2006b). Therefore, the exposure levels reported in this investigation must be interpreted with caution as they are likely conservative estimates of actual exposures in transportation environments. Nevertheless, the majority of particles produced by gasoline and diesel vehicles are between 0.02-0.1μm in diameter (Morawska and Zhang, 2002), and previous studies employing P-TRAKs have observed significant associations between UFP counts and oxidative DNA damage (Vinzents et al., 2005) as well as changes in heart rate variability (Chan et al., 2004) and vasoconstriction (Rundell et al., 2007). Therefore, while the P-TRAK is not the most sensitive instrument available, it remains a valuable instrument in environmental epidemiology owing to its portability and relatively low cost. Finally, our findings are limited in that our models were developed over a single transit route and do not consider the potential impact of vehicle ventilation settings (i.e. fan and recirculation) or factors such as vehicle speed or traffic counts/characteristics on UFP exposures in transportation environments. These limitations reduce the ability to generalize our findings as the models presented may not be suitable for use on transit routes with traffic characteristics different than those used for model development. For example, the models presented would likely overestimate UFP levels on transit routes with traffic counts lower than those used for model development and underestimate levels on routes with higher traffic counts. To address this issue, future studies should develop models over several different transit routes and include a "traffic count" variable in order to account for variations in UFP exposures owing to differences in traffic counts across routes. In doing so, traffic count data should be collected at several points along each transit route as the fixed-site measures used in

this study may not adequately represent traffic counts over the length of each route. In addition, future models should incorporate a variable for traffic characteristics as routes with a high percentage of large diesel vehicles are expected to have higher UFP levels than those used predominantly by smaller passenger vehicles. Likewise, the effects of vehicle ventilation should be explored in future models as some findings suggest that maximum in-cabin protection is provided when both fan and recirculation settings are operational (Zhu et al., 2007).

In general, UFP exposures observed in Montréal, Canada, are similar to those observed for UFP levels in buses and automobiles in Boston, Massachusetts (Levy et al., 2002), and slightly lower than those reported for buses in Birmingham, Alabama (Hammond et al., 2006). We observed lower UFP exposures while walking as compared to riding in buses or in the automobile, and this pattern was also reported in London, England (Kaur et al., 2005b; Kaur et al., 2006). In general, however, UFP exposures were greater in the English studies (Kaur et al., 2005b; Kaur et al., 2006). As in this study, previous investigations have observed higher UFP levels in the morning relative to the evening hours, and this effect may be attributed to lower mixing heights and lower wind speeds during the morning hours (Kuhlbusch et al., 2001) as well as factors such as higher engine temperatures in the evening hours (Fujita et al., 2007). In addition, traffic densities may be higher during the morning hours (Cyrys et al., 2003; Young and Keeler, 2004; Aalto et al., 2005; Kaur et al., 2005a; Kaur et al., 2005b; Kaur et al., 2006; Jeong et al., 2006) as the evening rush hour is generally more spread out relative to the morning commute. Indeed, differences in UFP exposures between London, England and Montréal, Canada might be explained in part by higher traffic densities in London, England, as the

traffic flow on the walk and bus routes in the English studies was estimated to be between 3000-3500 vehicles per hour (Kaur et al., 2005a; Kaur et al., 2005b; Kaur et al., 2006) compared to approximately 500 and 2000 vehicles per hour respectively for the walk and bus routes in the present study. The traffic density of the automobile route explored in the present study was similar to that included in two English studies (Kaur et al., 2005b; Kaur et al., 2006), and while comparable exposures were reported by one of these studies (Kaur et al., 2006) the other reported exposures nearly 3-times those observed in the current investigation (Kaur et al., 2005b). While the presence of strong local sources cannot be ruled out as the cause of this discrepancy, both English studies (Kaur et al., 2005b; Kaur et al., 2006) were conducted along the same route in the same type of gasoline-fueled automobile and thus dramatic differences in traffic density or vehicle characteristics are not expected. Alternatively, the observed difference might be explained in part by differences in temperature, wind speed, or mixing height as these variables were identified as significant determinants of UFP exposures in the current investigation. Indeed, Kaur et al. (2005b) reported only light winds (approximately 9 km/h) on sampling days which would tend to favor increased UFP exposures. Unfortunately, however, none of the three English studies (Kaur et al., 2005a; Kaur et al., 2005b; Kaur et al., 2006) reported data for these variables and as a result between-study comparisons of UFP exposures according to ambient weather conditions were not possible.

Diesel school buses and coach passenger buses were identified as strong local sources of UFPs while walking and driving respectively, and this observation is consistent with previous findings (Abraham et al., 2002; Levy et al., 2003; Westerdahl et

al., 2005). Interestingly, UFP exposures on public transit buses in Montréal were more than twice those reported for diesel school buses in Fredericton, New Brunswick (Health Canada, 2005); suggesting that traffic density likely (expected to be lower in Fredericton than in Montréal) plays an important role in determining in-vehicle exposures. Indeed, in this investigation increased UFP counts were observed when walking or driving from a quiet street onto a busier roadway (data not shown), and similar fluctuations in UFP exposures with traffic proximity have been reported previously (Kaur et al., 2006). Therefore, while diesel vehicles are strong local sources of UFPs, vehicle type alone is likely not a sufficient proxy for in-vehicle UFP exposures.

While we cannot rule out the potential influence of unmeasured confounding factors, significant inverse relationships were observed between temperature and wind speed and UFP exposures in walk, bus, and automobile environments. However, a high correlation between wind speed and mixing height meant that we could not estimate the independent effects of these two variables. Regardless, our findings are consistent with those of Vinzents et al (2005) who also observed a significant inverse relationship between temperature and wind speed and UFP exposures while bicycling in traffic. However, we were unable to identify other studies exploring the effects of ambient temperature and wind speed on UFP exposures in transportation environments. Nevertheless, previous studies have observed inverse relationships between wind speed and roadside UFP levels (Levy et al., 2003; Zhu et al., 2002; Zhu et al., 2006a) as well as between temperature and ambient UFP counts (Jeong et al., 2004; Jeong et al., 2006) and therefore our results appear to be consistent with previous findings. Indeed, lower UFP exposures were expected at increased wind speeds owing to the dispersion of vehicular

emissions, and the observed inverse correlation between ambient temperature and UFP exposures was not surprising as the formation of UFPs from traffic exhaust depends in part on vapor condensation (Korhonen et al., 2004; Kulmala et al., 2004) which is favored at lower temperatures. Specifically, some evidence suggests that organic compounds from unburned fuel and lubricating oil are involved in the formation of UFPs from vehicle exhaust (Tobias et al., 2001; Sakurai et al., 2003).

We observed no significant effect of window opening on UFP exposures in bus or automobile environments. However, it is possible that frequent bus door opening during passenger pick-up resulted in similar cabin ventilations on all sampling days thus masking the potential effects of bus window opening. Unfortunately, quantitative ventilation measures were not collected in buses or the automobile and more controlled exposure scenarios may be required for a comprehensive exploration of the effect of window opening on bus and automobile UFP exposures. Nevertheless, it seems likely that closed windows may reduce traffic related UFP exposures in buses and automobiles, particularly during encounters with large diesel vehicles which can result in substantial increases in cabin pollutants when windows are open (Behrentz et al., 2005; Sabin et al., 2005). In this respect, findings from the current study are consistent with those of previous investigations (Behrentz et al., 2005; Sabin et al., 2005) as dramatic increases in bus and automobile UFP levels were observed while driving past a coach passenger bus with the windows open (Figure 2B and 2C). However, other studies exploring the effects of window opening on UFP counts in buses or automobiles were not identified.

In this study, we observed no association between relative humidity and mean UFP exposures in transportation environments, and this is consistent with previous

findings reported for ambient UFP counts in Rochester, New York, and Detroit, Michigan (Young and Keeler, 2004; Jeong et al., 2006). However, one of these studies was conducted over a period of only 11-days, and the authors note that the low correlation may be due to the small range of observations and the presence of local sources during the study period (Young and Keeler, 2004). An inverse correlation was detected between relative humidity and ambient UFP concentrations in three European cities in which measurements were collected away from local traffic sources (de Hartog et al., 2005). Similarly, at least one previous study reported an inverse correlation between relative humidity and UFPs produced through photochemical nucleation (Jeong et al., 2006). Therefore, one explanation for the inverse correlations detected by de Hartog et al (2005) might be that photochemical processes were the primary sources of UFPs at the targeted sites. As such, the effect of relative humidity on UFP exposures may depend on the primary source of particles at a given measurement location, with relative humidity having little effect on traffic related UFP exposures and a negative effect on those resulting from photochemical processes.

Moderate to high correlations were observed between measured and predicted UFP exposures on new bus and automobile routes, with predictions for automobile UFP exposures generally outperforming those for UFP exposures on the new bus route. Specifically, model estimates tended to overestimate UFP levels in buses whereas the difference between measured and predicted UFP levels in the automobile was not statistically significant (Table 7). This finding may owe in part to higher traffic counts on the bus route used for model development (~ 2000 vehicles/hour) relative to the route used for model evaluation (~ 1000 vehicles/hour). Indeed, traffic counts on model

development and evaluation routes were approximately equal for the automobile and the observed difference between measured and predicted values was approximately half that observed for buses. Other investigations attempting to model UFP levels in transportation environments were not identified; however, our findings highlight the need to include variables such as traffic counts/characteristics and vehicle ventilation settings in future models as the inclusion of such factors may improve the predictive performance of the models presented.

Conclusions

Ultrafine particle exposures are a growing pubic health concern owing to increasing epidemiological and toxicological evidence suggesting that these particles may have an adverse effect on both cardiovascular and respiratory health. Vehicle traffic is a major source of UFPs, and as people spend an increasing proportion of their time commuting to and from work or school, the potential for exposure to harmful contaminants in these environments has also increased. In an 8-month sampling campaign conducted in Montréal, Canada, morning UFP exposures were significantly greater than those observed in the evening hours, and both ambient temperature and wind speed were significant determinants of UFP exposures in walk, bus, and automobile environments. However, we cannot rule out a potentially important effect for mixing height as a high correlation between wind speeds and mixing heights meant that we could not estimate the independent effects of these two variables. Further research is required to incorporate variables such as traffic counts and vehicle ventilation settings into the models presented. Once developed, these models may be useful in population-based studies interested in the potential health effects of UFP exposures.

Acknowledgements

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TABLES

Table 1. Summary of daily travel times in minutes for each transportation environment

	Mean (SD)	Minimum	Maximum
Morning			
Walk	8.44 (2.3)	3	16
Bus	10.6 (1.1)	8	15.5
Automobile	29.5 (6.1)	20.5	55
Evening			
Walk	4.31 (1.6)	3	10
Bus	17.9 (3.4)	11	33
Automobile	31.9 (6.5)	21	50

Abbreviation: SD, standard deviation.

Table 2. Summary of ambient weather conditions on sampling days

	Mean (SD)	Minimum	Maximum
Morning			
Temperature (°C)	13.1 (6.8)	-2	25.9
Relative humidity (%)	77.1 (13.1)	38	100
Wind speed (km/h)	12.7 (7.6)	0	35
Estimated mixing height (m)	4344 (2591)	178	12,414
Evening			
Temperature (°C)	18.0 (7.7)	1	33.6
Relative humidity (%)	60.9 (18.6)	21	99
Wind speed (km/h)	17.1 (7.6)	0	43
Estimated mixing height (m)	5849 (2538)	1240	15,135

Abbreviation: SD, standard deviation.

Table 3. Summary of UFP exposures (cm^{-3}) in each transportation environment

	Mean (SD)	GM (GSD)	Minimum [a]	Maximum [a]	95% CI
Morning					
Walk	25,161 (15,558)	21,216 (1.8)	5879	89,194	(21,698, 28,623)
Bus	28,029 (11,768)	25,684 (1.5)	8935	66,204	(25,410, 30,648)
Automobile	38,348 (16,000)	35,337 (1.5)	12,717	88,737	(34,787, 41,909)
Evening					
Walk	15,778 (7321)	14,740 (1.6)	4804	40,035	(14,149, 17,408)
Bus	22,626 (11,391)	20,500 (1.5)	6379	83,193	(20,091, 25,161)
Automobile	31,489 (11,976)	29,558 (1.4)	16,279	72,913	(28,824, 34,154)

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; CI, confidence interval.
[a] Minimum/maximum daily average UFP exposure (cm^{-3}) in each micro-environment

Table 4. Multivariable models for morning UFP exposures (cm^{-3})

Independent Variables	Model coefficients			
	α	95% CI	β	95% CI
Walking	452,665	(353,468, 551,861)		
Temperature (K)			-1456	(-1802, -1111)
Wind speed (km/h)			-825	(-1136, -513)
Bus	269,633	(180,617, 358,650)		
Temperature (K)			-816	(-1126, -506)
Wind speed (km/h)			-621	(-900, -342)
Automobile	371,192	(242,835, 499,549)		
Temperature (K)			-1131	(-1581, -682)
Wind speed (km/h)			-635	(-1026, -244)
Windows open			-5585	(-14,176, 3005)

Abbreviation: CI, confidence interval

Table 5. Multivariable models for evening UFP exposures (cm^{-3})

Independent Variables	Model coefficients			
	α	95% CI	β	95% CI
Walking	146,539	(91,599, 201,479)		
Temperature (K)			-444	(-633, -254)
Wind speed (km/h)			-82	(-273, 108)
Bus	74,176	(-32,306, 108,658)		
Temperature (K)			-130	(-514, 252)
Wind speed (km/h)			-463	(-779, -149)
Windows open			-6250	(-15,055, 2554)
Automobile	171,170	(83,534, 258,807)		
Temperature (K)			-446	(-748, -143)
Wind speed (km/h)			-632	(-939, -326)
Windows open			4531	(-1123, 10,186)

Abbreviation: CI, confidence interval

Table 6. Multivariable models for UFP exposures (cm^{-3}) over all transit periods combined

Independent Variables	Model coefficients			
	α	95% CI	β	95% CI
Walking	294 051	(235,981, 352,122)		
Morning Time Period			2169	(-973, 5312)
Temperature (K)			-932	(-1132, -732)
Wind speed (km/h)			-404	(-595, -213)
Temp_c*Wind speed_c [a]			58	(34, 83)
Bus	184 900	(124,875, 244,925)		
Temperature (K)			-525	(-735, -316)
Wind speed (km/h)			-519	(-721, -316)
Automobile	275,979	(205,380, 346,578)		
Temperature (K)			-805	(-1051, -559)
Wind speed (km/h)			-575	(-813, -339)
Temp_c*Wind speed_c [a]			19	(-13, 51)

Abbreviation: CI, confidence interval

[a] Interaction term for temperature (K) and wind speed (km/h) using centered variables

Table 7. Summary of observed and predicted bus and automobile UFP exposures (cm^{-3}) on different transit routes

Transportation Environment	Observed UFP exposure			Predicted UFP exposure		Difference [a]	
	N	Mean	95% CI	Mean	95% CI	Mean	95% CI
Bus	42	27,530	(22,332, 32,728)	33,820	(31,702, 35,937)	-6289	(-11,818, -761)
Automobile	22	55,155	(45,495, 64,815)	51,615	(46,233, 56,996)	3540	(-7190, 14,271)

Abbreviation: CI, confidence interval

[a] Observed – Predicted.

FIGURES

Figure 1. Box-plots for mean morning and evening UFP exposures (cm^{-3}) in each transportation environment.

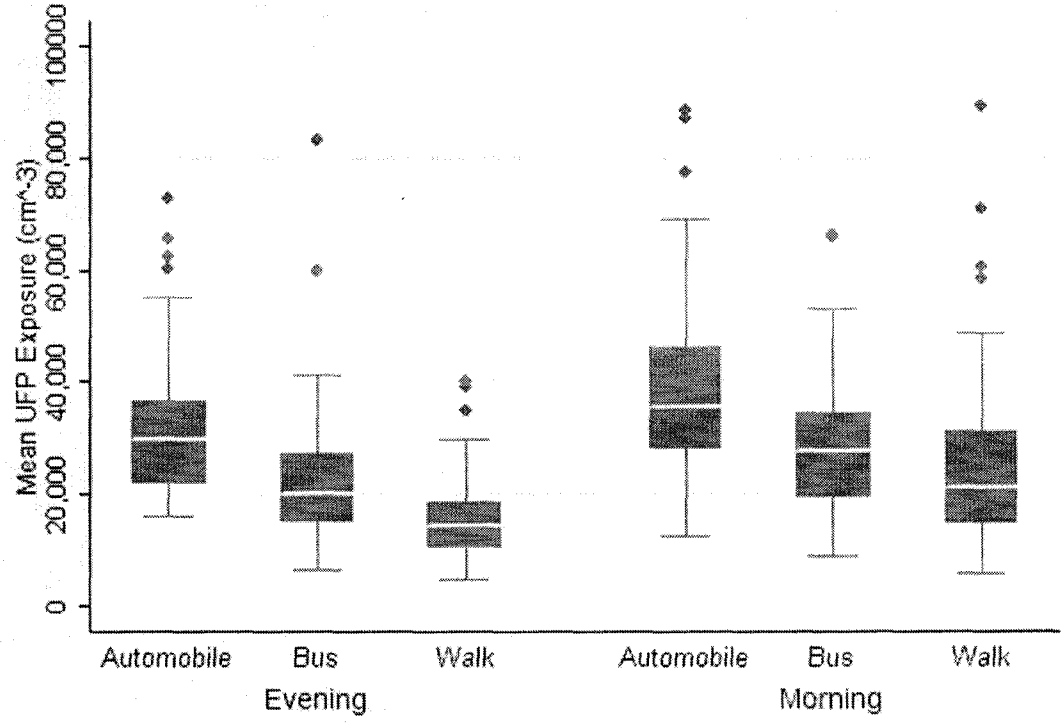


Figure 2a. Observed increase in UFP exposure while walking past an idling school bus.

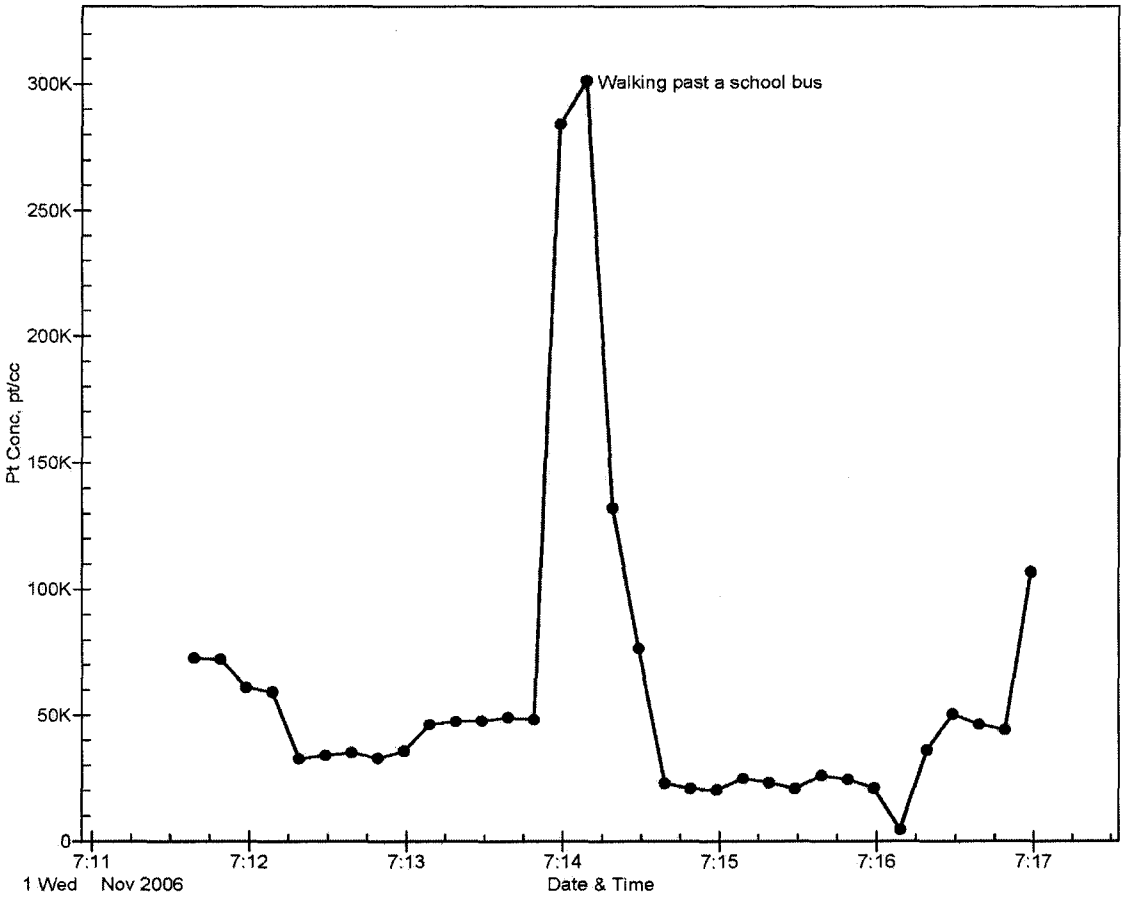


Figure 2b. Observed increase in UFP exposure while driving next to a coach passenger bus in a public transit bus with windows open.

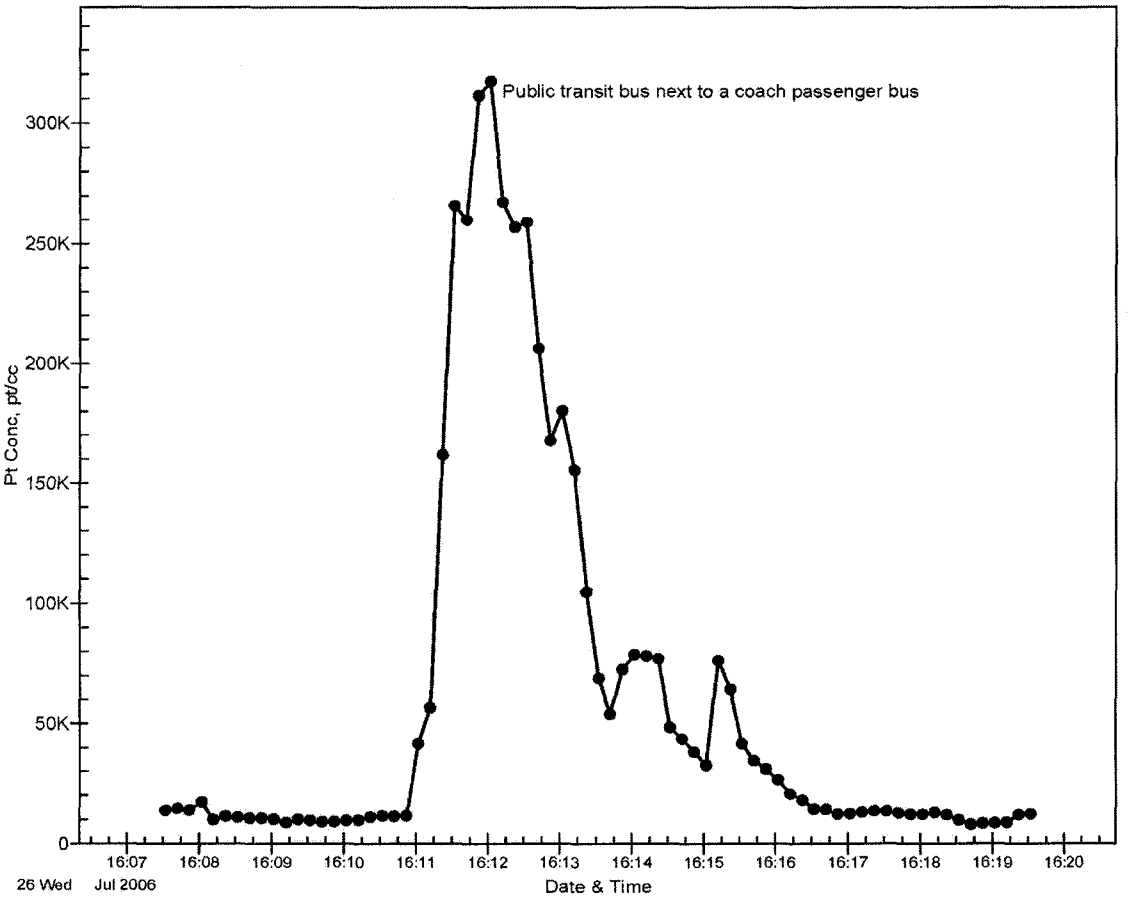


Figure 2c. Observed increase in UFP exposure while driving next to a coach passenger bus in an automobile with windows open.

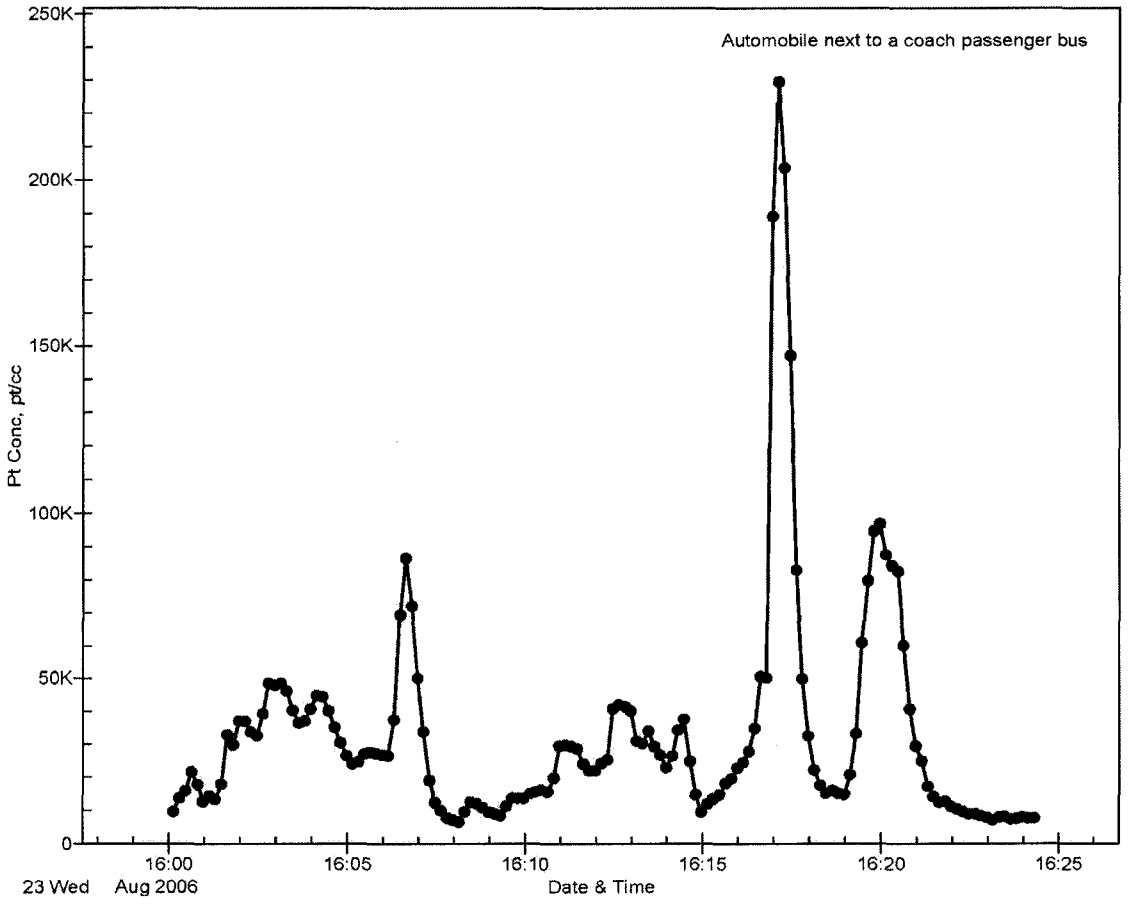


Figure 3a-1. Scatter-plot of temperature and mean UFP exposures while walking.

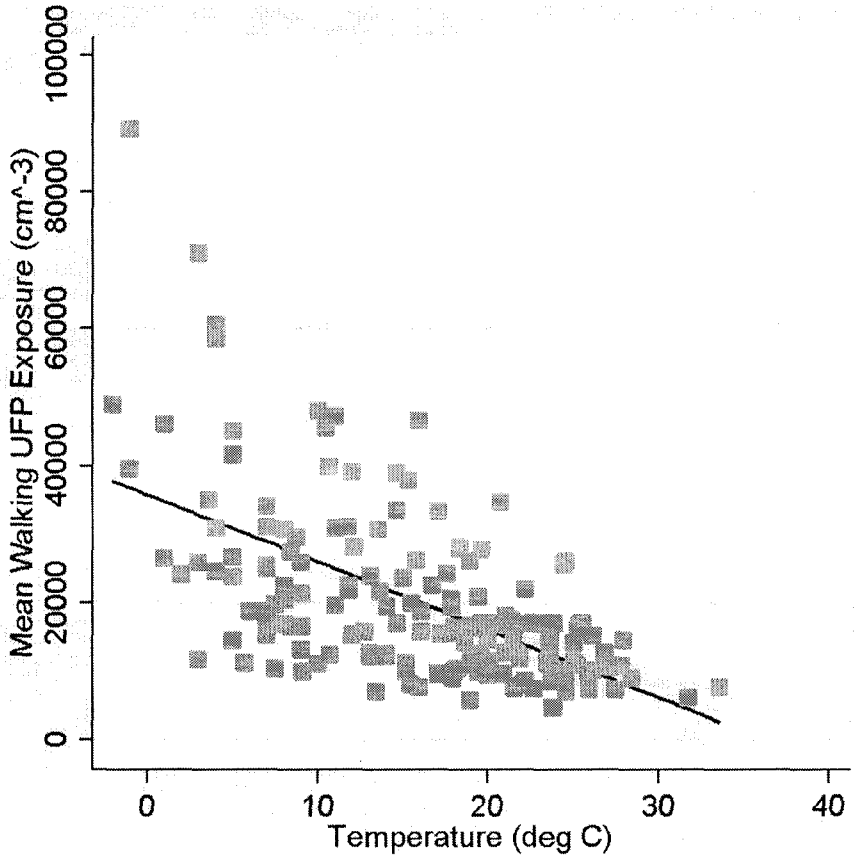


Figure 3a-2. Scatter-plot of temperature and mean UFP exposures while riding in a public transit bus.

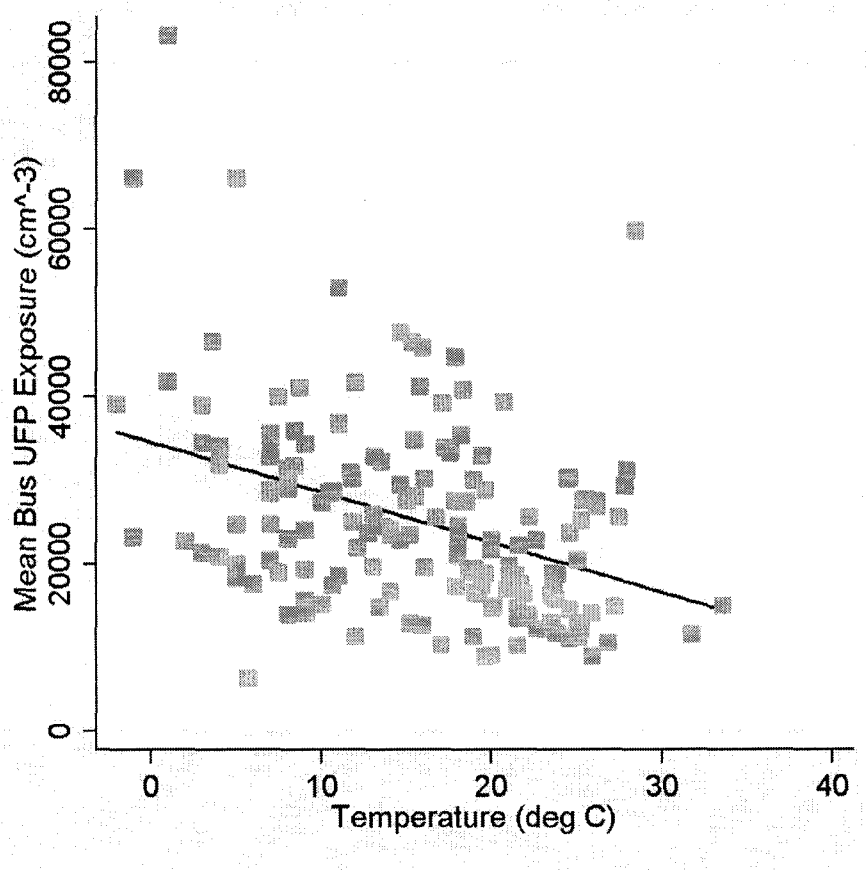


Figure 3a-3. Scatter-plot of temperature and mean UFP exposures while riding in an automobile.

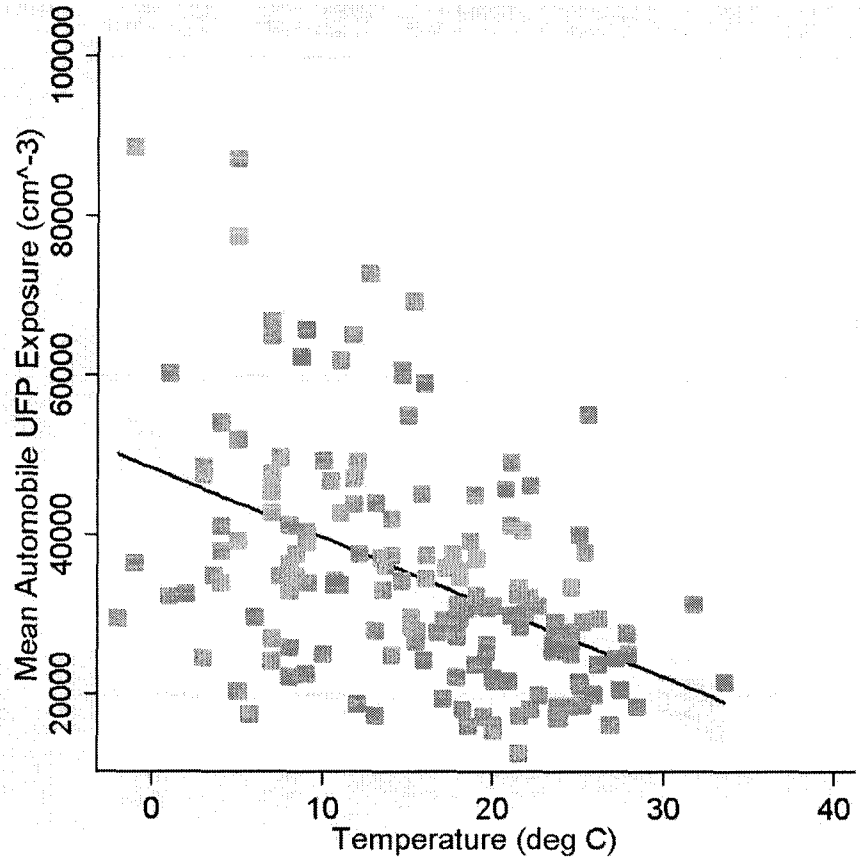


Figure 3b-1. Scatter-plot of wind speed and mean UFP exposure while walking.

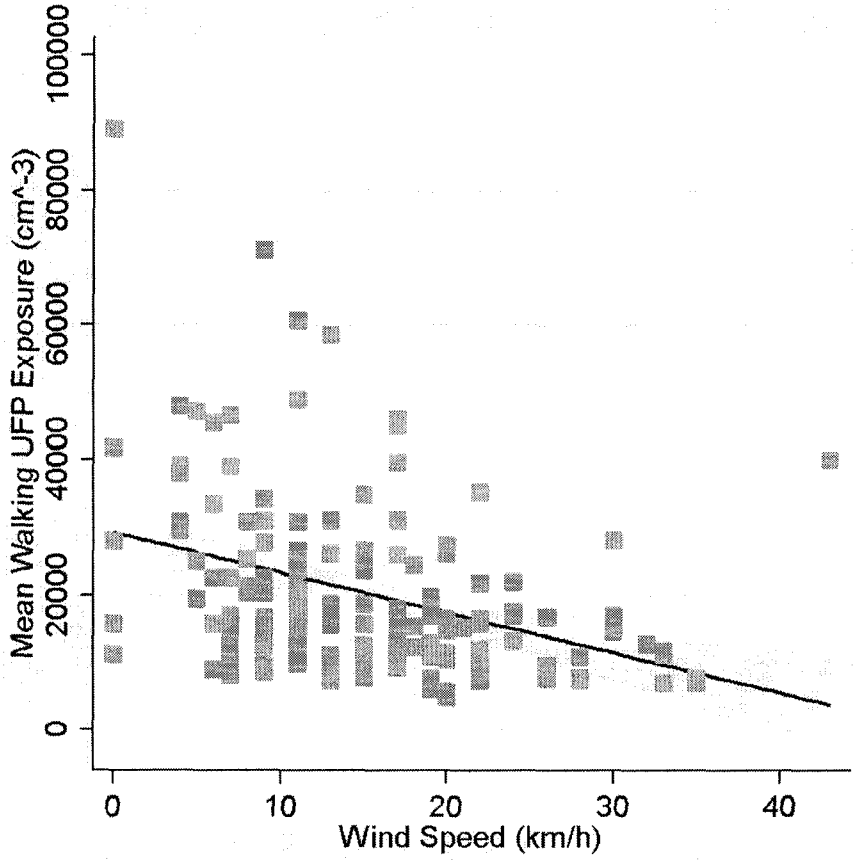


Figure 3b-2. Scatter-plot wind speed and mean UFP exposure while riding in a public transit bus.

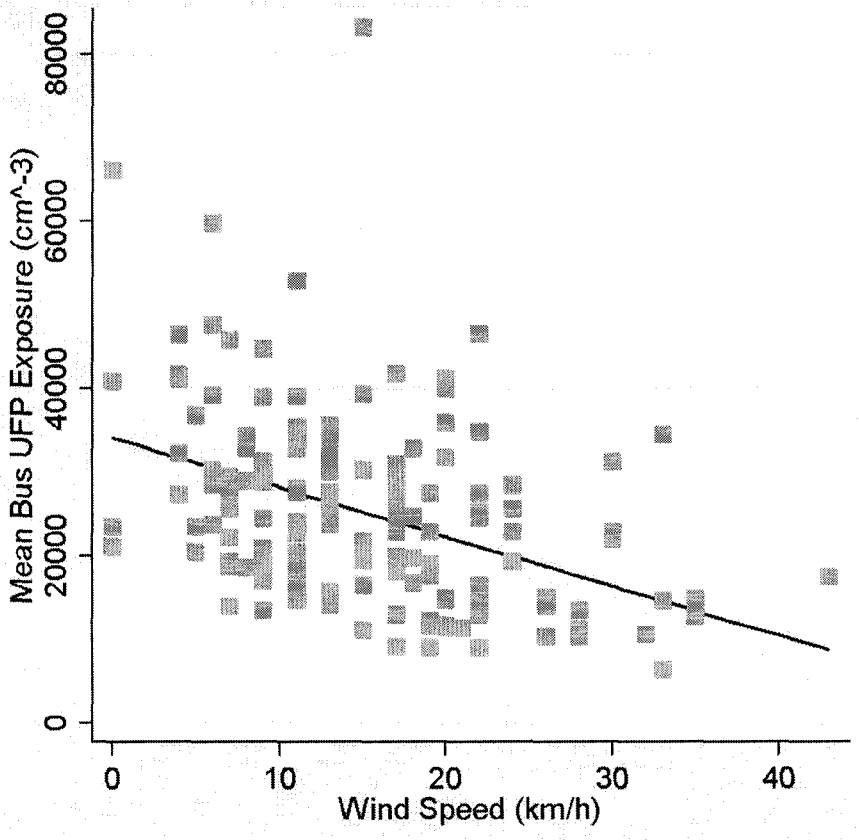


Figure 3b-3. Scatter-plots wind speed and mean UFP exposure while riding in an automobile.

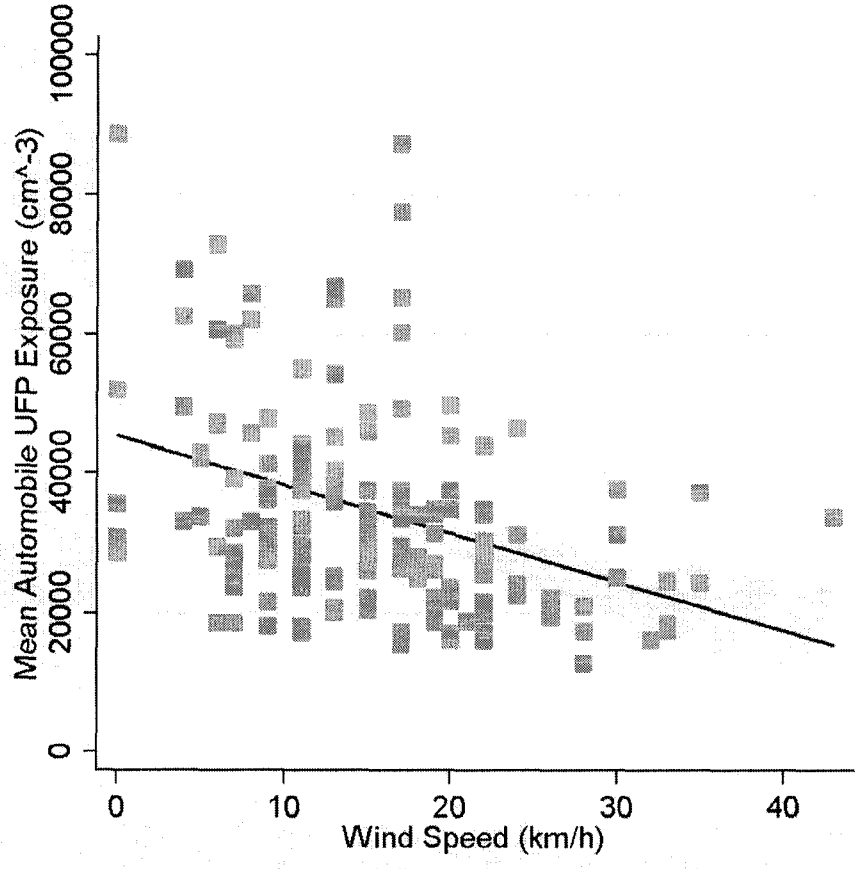


Figure 4a. Correlation between measured and predicted UFP exposures on a different automobile route (two outliers removed).

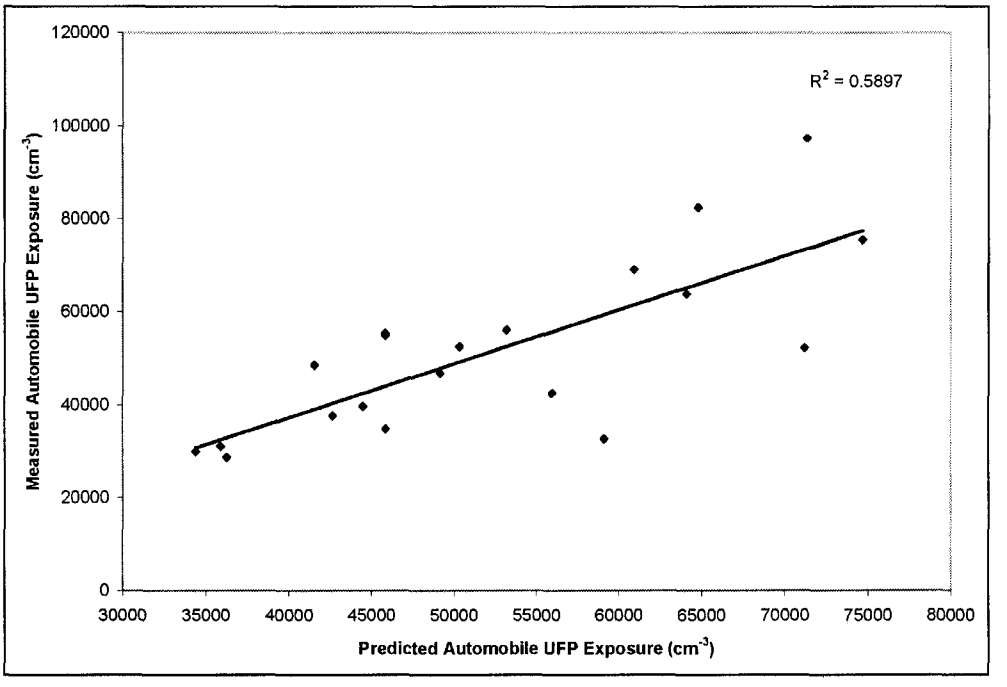
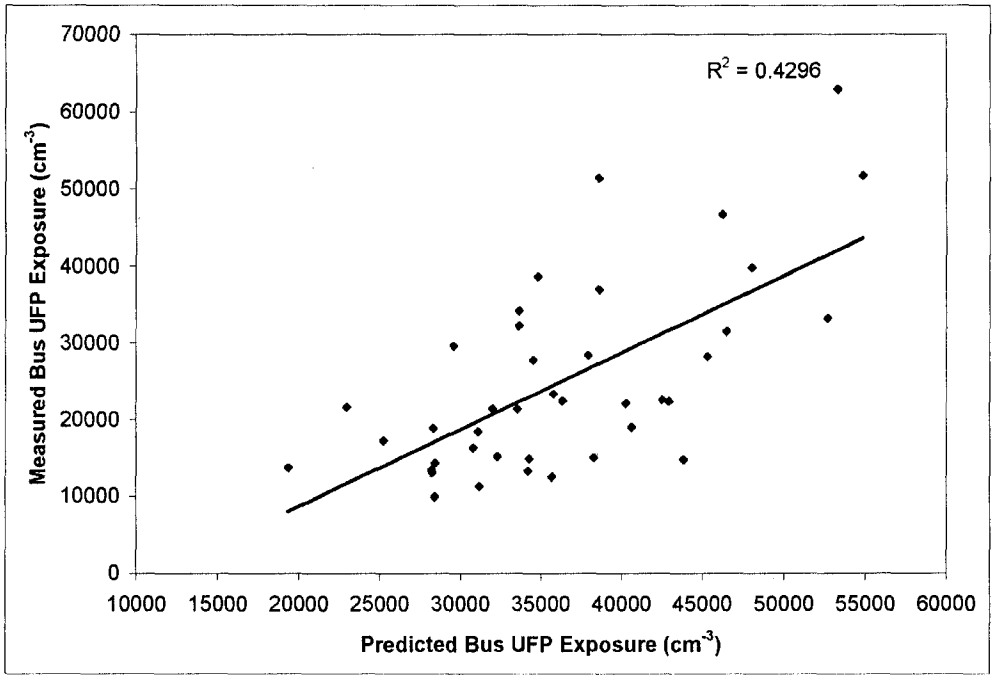


Figure 4b. Correlation between measured and predicted UFP exposures on a different bus route (two outliers removed).



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4.1 PREFACE TO MANUSCRIPT D

When not at home school-age children spend the majority of their time in classrooms, and as such exposures in these locations may have a considerable impact on children's cumulative UFP exposures. Few studies have examined UFP exposures in schools to date, particularly during the winter months when classroom windows are kept closed and overall air quality is generally poor. Furthermore, little is known about determinants of UFP exposures in schools as we could not identify any studies which have attempted to model such exposures. As a result, we conducted a cross-sectional survey during winter 2007 in order to characterize UFP levels in Canadian classrooms and to develop a model to predict such exposures based on ambient weather conditions and outdoor UFPs as well as classroom characteristics such as size, temperature, relative humidity, and carbon dioxide levels. Four schools were included in our study: two were used to develop a model to predict classroom UFP levels while the other two schools were used to test the model. A manuscript describing the findings of this investigation is presented next.

5. MANUSCRIPT D

CHARACTERIZING AND PREDICTING ULTRAFINE PARTICLE COUNTS IN CANADIAN CLASSROOMS DURING THE WINTER MONTHS

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Human subjects were not directly involved in this study, but informed written consent was obtained from school authorities prior to in-school monitoring.

Abstract

School classrooms are potentially important micro-environments for childhood exposures owing to the large amount of time children spend in these locations. While a number of airborne contaminants may be present in schools, to date few studies have examined ultrafine particle (0.02-1μm) (UFP) levels in classrooms. In this study, our objective was to characterize UFP counts (cm^{-3}) in classrooms during the winter months and to develop a model to predict such exposures based on ambient weather conditions and outdoor UFPs, as well as classroom characteristics such as size, temperature, relative humidity, and carbon dioxide levels. In total, UFP count data were collected on 60 occasions in 37 occupied classrooms at one elementary school and one secondary school in Pembroke, Ontario. On average, outdoor UFP levels exceeded indoor measures by 8989 cm^{-3} (95% Confidence Interval (CI): 6382, 11 596), and classroom UFP counts were similar at both schools with a combined average of 5017 cm^{-3} (95% CI: 4300, 5734). Of the variables examined only wind speed and outdoor UFPs were important determinants of classrooms UFP levels. Specifically, each 10 km/h increase in wind speed corresponded to an 1873 cm^{-3} (95% CI: 825, 2920) decrease in classroom UFP counts, and each 10 000 cm^{-3} increase in outdoor UFPs corresponded to a 1550 cm^{-3} (95% CI: 930, 2171) increase in classroom UFP levels. However, high correlations between these two predictors meant that the independent effects of wind speed and outdoor UFPs could not be separated in multivariable models, and only outdoor UFP counts were included in the final predictive model. To evaluate model performance, classroom UFP counts were collected for 8 days at two new schools and compared to predicted values based on outdoor UFP measures. A moderate correlation was observed

between measured and predicted classroom UFP counts ($r = 0.63$) for both schools combined, but this relationship was not valid on days in which a strong indoor UFP source (electric kitchen stove) was active in schools. In general, our findings suggest that reasonable estimates of classroom UFP counts may be obtained from outdoor UFP data but that the accuracy of such estimates are limited in the presence of indoor UFP sources.

Key words: School air quality; Particulate matter; Ultrafine particles; Exposure modeling.

1. Introduction

Indoor air quality has a considerable impact on public health (Jones, 1999), and for school-age children classroom air quality is particularly important owing to the large amount of time children spend in these locations. A number of indoor air pollutants have been measured in school buildings including volatile organic compounds (VOCs), carbon dioxide, formaldehyde, nitrogen dioxide, and various biological contaminants (Lee and Chang, 1999; Scheff et al., 2000a; Bartlett et al., 2004; Scheff et al., 2000b; Shendell et al., 2004a; Blondeau et al., 2005; Ramachandran et al., 2005; Godwin and Batterman, 2006). In addition, some evidence suggests that these types of exposures may have an adverse effect on student health, attendance, and/or academic performance (Daisey et al., 2003; Shendell et al., 2004b; Mendell and Heath, 2005; Mi et al., 2006; Shaughnessy et al., 2006). While exposure to ambient particulate matter (PM) is known to have a negative impact on respiratory health in both children and adults (Pekkanen et al., 1997; Peters et al., 1997; Tiittanen et al., 1999; Penttinen et al., 2001a; Penttinen et al., 2001b; Von Klot et al., 2002), little is known about the potential health effects of indoor PM exposures. Recently, increased attention has focused on the potential respiratory effects of indoor ultrafine particles (UFP) (Weichenthal et al., 2007a) as they are known to trigger oxidative stress and inflammation in the lungs (Oberdörster et al., 1994; Li et al., 1996; Afaq et al., 1998; Zheng et al., 1998; Brown et al., 2001; Dick et al., 2003; Li et al., 2003; Gilmour et al., 2004). However, studies examining PM levels in classrooms have generally focused on either fine ($PM_{2.5}$) or course (PM_{10}) particles (Janssen et al., 1999; Scheff et al., 2000a; Keeler et al., 2002; Blondeau et al., 2005; Braniš et al., 2005; Fromme et al., 2006) and to date only two studies have reported UFP counts in school

classrooms (Fromme et al., 2006; Diapouli et al, 2007). As such there is currently a need to characterize UFP levels in classrooms, particularly during the winter months when room ventilation and overall air quality tend to be lowest. In addition, cost-effective methods of estimating indoor UFP exposures are required if we hope to explore the potential health effects of such exposures in population-based studies (Sioutas et al., 2005).

The primary objective of this study was to characterize UFP counts (cm^{-3}) in school classrooms during the winter months and to develop a model to predict such exposures based on ambient weather conditions and outdoor UFP levels as well as classroom characteristics such as size, temperature, relative humidity, carbon dioxide levels, and ventilation. Mass concentrations for $PM_{2.5}$ in schools are also reported, and the correlation between measured and predicted UFP counts in classrooms is evaluated. As a secondary objective, the relationship between outdoor UFP counts and ambient weather data is also explored.

2. Methods

2.1 School characteristics

In November 2006, officials at two schools in Pembroke, Ontario were contacted by telephone and following an explanation of the study were invited to participate. Each school was identified opportunistically and the first two schools contacted agreed to participate. Neither school had previously reported complaints with respect to indoor air quality. School A is a primary school with approximately 300 students and is located on a corner lot with light traffic flow on two sides of the school building. School B is a secondary school with approximately 1100 students and is located at the end of a cul-de-sac used by local traffic only. Classrooms at School A are supplied with mechanical ventilation whereas School B is naturally ventilated with the exception of two science labs which have mechanical ventilation. Both schools are heated with hot-water radiators supplied by natural gas boilers and the two schools are separated by a distance of approximately 2-kilometers. In addition to the main school building, each school has one portable type classroom that is used on a regular basis. Portable classrooms are heated with electric baseboard heaters and are naturally ventilated with the exception of a small wall-mounted exhaust fan that is seldom used. All classrooms have tile flooring and occupancies range from 17 to 23 at School A and 10 to 25 at School B.

2.2 Data collection

Between January and March 2007, School A and B were each visited for three 1-week periods and two different classrooms were monitored in the same school on each sampling day. All UFP, temperature, relative humidity, and carbon dioxide data were collected in occupied classrooms for approximately 7-hours between 8:30 a.m. and 3:30 p.m., and all instruments were placed approximately 1-meter above classroom floors away from windows and doors. Fine particle mass samples ($PM_{2.5}$) were collected at the same time as classroom samples in the gymnasium in School A and in a hallway in School B because the sampling pump was too loud to place in classrooms.

Mean outdoor temperature, relative humidity, and wind speed data were recorded from local monitoring stations during each sampling period and the volume (m^3) of each classroom was estimated using floor dimensions and ceiling height. In addition, teachers were asked about the predominant classroom window position (open or closed) throughout the day.

Ultrafine particle counts (cm^{-3}) were recorded in classrooms at 10-second sampling intervals using TSI P-TRAK 8525 Ultrafine Particle Counters (TSI, Shoreview, MN, USA). These instruments are condensation particle counters with continuous data-logging capabilities and are capable of detecting particles between approximately 0.02-1μm. Outdoor UFP count data was collected for each school at the beginning and end of each sampling day. To do this, P-TRAK readings were allowed to stabilize for approximately 2-minutes and then a 10-second average value for outdoor UFPs was recorded. It was not possible to collect outdoor UFP count data for extended periods of time because outdoor temperatures were generally below the minimum recommended

operating temperature of 0°C for the P-TRAK. All indoor UFP measures reflect time-weighted average number concentrations, and both P-TRAKs were calibrated by the manufacturer prior to sampling and were zero checked and equipped with a newly recharged alcohol wick each day. In side-by-side comparisons, no notable difference was observed between the UFP counts reported by the two instruments used in this study.

Classroom temperature, relative humidity, and carbon dioxide levels were monitored using a TSI Q-TRAK (TSI, Inc, Shoreview, MN, USA) indoor air quality monitor programmed to collect data at 1-minute intervals. The Q-TRAK was calibrated by the manufacturer prior to sampling, and in addition the carbon dioxide sensor was calibrated daily using zero grade air and a 1000 parts per million (p.p.m) CO_2 standard. Outdoor carbon dioxide levels were also recorded each morning with the same instrument to correct indoor levels used in air exchange rate estimates for background concentrations. As only one Q-TRAK was available throughout the study period, the instrument was placed in each of the two classrooms monitored daily for half a day each (approximately 3.5 hours).

Classroom air exchange rates (h^{-1}) (Ach) were estimated using real-time measures of indoor carbon dioxide according to the following relationship:

$$Ach = \frac{\ln C_o - \ln C_t}{\Delta T} \qquad [1]$$

For this calculation, an initial indoor carbon dioxide concentration (C_o) was selected such that the time needed (ΔT) for a continuous linear decay to a lower concentration (C_t) was maximized throughout the sampling period. To correct for the background contribution of outdoor carbon dioxide, ambient concentrations were subtracted from the initial and final

concentrations used in the above equation. Typically, air exchange rates were based on the decay of carbon dioxide in classrooms once students had left rooms for lunch or at the end of the day.

Indoor $PM_{2.5}$ measures were collected using a Sioutas cascade impactor fitted with 25-mm Teflon filters (0.5 μm pore size) and a Leland Legacy (SKC, Inc, Eighty Eight, PA) pump at 9 L/min. Samplers were calibrated before and after each sampling run with a certified DryCal DC-Lite primary flow meter (Bios, Inc, Butler, NJ) and the average of the two flow rates was used to determine the volume of air sampled each day. Five field blanks were collected by loading the impactor with a filter and removing it without running the pump and the mean field blank weight change was subtracted from all sample weights. All filters were stored in sealed 50-mm Petri dishes and were conditioned in a desicator for 48 hours before weighing. Each filter was weighed twice before and after sampling using a Mettler AE163 microbalance with 10 μg reading accuracy and the average weight was recorded (Mettler-Toledo, Columbus, Ohio). Detection limits for $PM_{2.5}$ were estimated to be 9.8 $\mu g/m^3$ and 8.5 $\mu g/m^3$ for Schools A and B, respectively based on three times the standard deviation of field blanks divided by the mean sample volume. Values lower than the detection limits were entered as one-half the detection limit for each school.

2.3 Additional data collection for model evaluation

In March 2007, two additional schools were identified in order to test the model developed in Schools A and B. Two different schools in Pembroke, Ontario were contacted by telephone and following an explanation of the study were invited to participate. The first two schools contacted (School C and School D) agreed to participate and in April 2007 indoor and outdoor UFP counts as well as ambient temperature and wind speed data were recorded at these schools for a total of 8 days each. UFP data was collected in one occupied classroom in each school and the volumes of these classrooms are approximately 308 m^3 and 255 m^3 for Schools C and D respectively. Classrooms in Schools C and D are supplied with mechanical ventilation and are heated by natural gas boilers. Only light traffic flow is present outside Schools C and D and all schools are located within 5 kilometers of one another.

2.4 Statistical analysis

All descriptive statistics, simple linear models, box-plots, R^2-values, Spearman's correlation coefficients (r_s), and scatter-plots were generated using the statistical software package STATA version 9.1 (Statacorp, College Station, TX, USA). Real-time plots of UFPs were produced using Trak Pro software available from TSI (TSI Inc., Shoreview, MN, USA) and scatter-plots of measured and predicted UFP counts were generated using Microsoft Excel 2003. To account for repeated measures in some classrooms, hierarchical models were run using the free software package WinBUGS (Spiegelhalter et al., 2002). Since only small changes in estimates were observed between hierarchical and non-hierarchical models, only the non-hierarchical model results are reported here.

The relationship between classroom UFP counts and indoor/outdoor temperature and relative humidity, wind speed, carbon dioxide, outdoor UFPs, air exchange rate, classroom volume, and classroom window position was assessed in linear models using data from Schools A and B combined. A dichotomous "school" parameter was also included in these models and pair-wise correlations between independent variables were assessed using Spearman's correlation coefficients. In all models, temperature (K), relative humidity (%), wind speed (km/h), carbon dioxide (p.p.m), air exchange rate (h^{-1}), outdoor UFPs (cm^{-3}), and classroom volume (m^3) were treated as continuous variables whereas window position was treated as a dichotomous variable (open/closed). When exploring the relationship between classroom UFP counts and indoor temperature, relative humidity, and carbon dioxide, data were organized to reflect the time period in which the Q-TRAK and P-TRAK were present simultaneously in the classroom. This was necessary because the Q-TRAK was present in classrooms for half of each school day whereas P-TRAKs were present in classrooms for the entire school day.

Interaction between independent variables in final models was assessed through the inclusion of first order interaction terms. Centered variables were used to create interaction terms in order to reduce correlations between interaction terms and independent variables. In selecting a final model, Bayesian Model Averaging (BMA) was employed using the statistical software package R version 2.4.0 (R Development Core Team, 2003). Bayesian model averaging is advantageous because final model coefficients reflect a weighted average of all possible models weighted by the probability that each model is correct, thus accounting for model uncertainty (Kass and Raftery, 1995; Wasserman, 2000). In addition, Bayesian model selection has been shown to out-

perform stepwise methods of model selection in making future predictions (Wang et al., 2004), as over-fitting is generally avoided. As such, predicted values for UFP counts in classrooms from Schools C and D were generated using final multivariable models selected by BMA and generated using data from Schools A and B combined. The correlation (r) between measured and predicted UFP counts in classrooms was then assessed in a simple linear model and was calculated as the square root of the coefficient of determination (R^2).

As a secondary objective, the relationship between outdoor UFP counts and ambient weather data was also explored using the statistical approach described above. Such a relationship was of interest because it may be used in population-based studies to estimate UFP counts outside of schools when quantitative data is not available.

3. Results

In total, UFP count data were collected on 60 occasions in 37 different classrooms for a mean (standard deviation) duration of 6.4 (1.2) hours. At School B, twenty-five regular classrooms were monitored once and one portable classroom was monitored on five separate occasions. At School A, six regular classrooms and one portable classroom were monitored three times and four regular classrooms were monitored twice throughout the sampling period. Data for classroom temperature, relative humidity, and carbon dioxide were not available for two days at School A and one day at School B owing to operator error. In addition, it was not possible to estimate air exchange rates for three days at School A and four days at School B because of lost data owing to operator error or the absence of a sustained drop in classroom carbon dioxide levels throughout the sampling period. Classroom windows were generally kept closed, with teachers reporting open windows on only four sampling days.

Summary statistics for indoor and outdoor measures are shown in Table 1. Outdoor UFP levels were similar at both schools, with levels outside School A on average exceeding those at School B by 1740 cm^{-3} (95% CI: -3354, 6834). Classroom UFP levels were slightly greater at School A (mean difference= 823 cm^{-3}, 95% CI: -607, 2253), and the combined average for classroom UFP counts at both schools was 5017 cm^{-3} (95% CI: 4300, 5734). Outdoor UFP counts were on average 9448 cm^{-3} (95% CI: 6123, 12 772) greater than classroom levels at School A, and 8531 cm^{-3} (95% CI: 4414, 12 647) greater than classroom levels at School B, with combined outdoor levels exceeding combined indoor levels by 8989 cm^{-3} (95% CI: 6382, 11 596); indicating the absence of significant indoor UFP sources at both schools.

Classroom carbon dioxide levels often exceeded the ASHRAE (American Society of Heating and Refrigerating and Air-conditioning Engineers) Standard of 1000 p.p.m (ASHRAE, 1989) at both schools, with corresponding outdoor carbon dioxide levels ranging from 347 to 420 p.p.m. Classroom relative humidity tended to be low, particularly in one classroom at School B which contained approximately twenty personal computers (RH=9.8%).

Of the fifteen $PM_{2.5}$ samples collected in the gymnasium at School A, two were discarded owing to pump failure and of the remaining thirteen samples three were below the detection limit. One $PM_{2.5}$ sample was discarded from School B because of pump failure, and of the remaining fourteen samples seven were below the detection limit. Therefore, $PM_{2.5}$ levels tended to be low in the locations monitored at each school with average values falling below Health Canada's indoor guideline of 40 $\mu g/m^3$ (Health Canada, 1989). Only two measures collected in the gymnasium of School A exceeded this value and these values were 60.3 $\mu g/m^3$ and 78.7 $\mu g/m^3$.

3.1 Relationship between indoor and outdoor variables and classroom UFP counts

Single-variable regression models for the relationship between classroom UFP counts and the indoor/outdoor variables measured are shown in Table 2. Wind speed and outdoor UFP counts were significant determinants of classroom UFP levels, with wind speed showing an inverse association with classroom UFP counts (Figure 1) and outdoor UFP counts showing a positive association with classroom UFP levels (Figure 2). Real-time measures confirmed the tendency for classroom UFP counts to increase with increased infiltration of outdoor air, and this effect is depicted in Figure 3 for School A.

In this figure, increases in classroom UFP counts are apparent when school doors are opened in the morning and at break periods.

While only a small number of UFP measures were collected in portable classrooms, classroom type was not an important determinant of classroom UFP levels when explored in a linear model (β = -240, 95% CI: -2372, 1891) (coefficient for UFPs in regular versus portable classrooms). In addition, no statistically significant effect was observed for the "school" variable included in linear models.

3.2 Relationship between outdoor UFP counts and ambient weather conditions

Single-variable regression models for the effects of ambient temperature, relative humidity, and wind speed on outdoor UFP counts are shown in Table 3. Wind speed and ambient temperature were each inversely associated with outdoor UFP counts (Figure 4 and Figure 5), with the effect of wind speed exceeding that of ambient temperature. However, no meaningful relationship was detected between relative humidity and outdoor UFP levels.

3.3 Predictive models for classroom and outdoor UFP counts

The combined effect of wind speed and outdoor UFP levels on classroom UFP counts was assessed in a multivariable model. However, wind speed was inversely associated with outdoor UFPs (r_s = -0.64) and the coefficient for wind speed decreased substantially when both variables were included in the same model. As such, outdoor UFP counts alone were included in the final predictive model for classroom UFPs and this model is shown in Table 4 (*Indoor model*).

The combined effect of ambient temperature and wind speed on outdoor UFP counts was also assessed in a multi-variable model, and while a small correlation was

detected between these two variables (r_s = -0.22), coefficients remained stable when both variables were included in the same model. In addition, a significant interaction was observed between ambient temperature and wind speed. The final predictive model for outdoor UFPs is shown in Table 4 (*Outdoor model*).

3.4 Relationship between measured and predicted classroom UFP counts

On average, monitoring days for Schools C and D were warmer (mean temperature = 2.9°C) and less windy (mean=9.8 km/h) for than those for Schools A and B, and an indoor source was present in School D for three of the eight sampling days, which resulted in short-term peak (approximately 1-hour) classroom UFP levels ranging from 65 000 cm^{-3} to 175 000 cm^{-3} (data not shown). This source was later identified as an electric kitchen stove located in a classroom approximately four rooms away from the classroom monitored. Classroom windows were closed during sampling at both schools.

In general, model estimates overestimated classroom UFP counts at School C and underestimated classroom UFP counts by at School D (Table 5). For both schools combined, a moderate correlation (r = 0.63) (Figure 6) was observed between measured and predicted classroom UFP counts after the removal of three outlying data points collected in School D on days in which the indoor UFP source was active. When these points were kept no correlation was observed between measured and predicted classroom UFP counts (r = 0.0). A moderate correlation (r = 0.63) was also observed for measured and predicted outdoor UFP counts for both schools combined, and this correlation increased further with the removal of one outlying data point for which no clear cause was identified (r = 0.79) (Figure 7). However, model estimates for outdoor UFPs were generally less accurate than those for indoor UFP counts (Table 5).

4. Discussion

Ultrafine particle counts were monitored in 37 classrooms on 60 occasions, and to our knowledge this is the first study to explore determinants of UFP counts in schools during the winter months. However, our findings are limited in that outdoor UFP measures were collected for only a short time-period outside each school and we have no information concerning the chemical composition of UFPs in classrooms. In addition, we do not have data concerning the number-weighted size distribution of UFPs which may be used in source apportionment models to identify important sources of indoor UFPs (Ogulei et al., 2006). However, with the exception of an electric kitchen stove in School D, strong indoor UFP sources were not identified in the schools examined. Another limitation of our study included the instrumentation employed which could not detect particles below 0.02 μm. As a result, it is possible that classroom UFP counts were underestimated because the combustion of natural gas (e.g. in school boilers) is known to produce UFPs below this size limit (Wallace, 2000). In addition, our findings reflect classroom UFP levels in a rural area of Canada and may not represent classroom levels in schools located in urban areas or close to high-traffic roadways. Finally, data collection for the model evaluation portion of this investigation was conducted over a short two-week period in spring and ideally would have been conducted concurrently with winter measures to ensure similar environmental conditions during model development and application. However, this was not possible owing to the limited number of instruments available. Therefore, as the number of classrooms examined was relatively small, future studies should aim to include a larger number of schools to further explore determinants of classroom UFP levels.

While $PM_{2.5}$ levels in schools were generally low, classroom carbon dioxide levels often exceeded the ASHRAE Standard of 1000 p.p.m (ASHRAE, 1989). However, our findings may not represent typical values throughout the school year as classroom carbon dioxide levels are expected to be lower during warmer months when windows are generally kept open. Nevertheless, previous studies have reported classroom carbon dioxide concentrations similar to those observed in the current investigation (Fromme et al., 2006; Mi et al., 2006; Godwin and Batterman, 2006) and our findings suggest that many of the classrooms monitored had inadequate fresh air supply during the winter months.

Two previous studies have reported UFP counts in classrooms. The first of these two investigations examined UFP counts in 36 classrooms in Germany during the summer months and reported a median classroom UFP count (5660 cm^{-3}) (Fromme et al., 2006) similar to that observed in the present study. Alternatively, a second study conducted in 11 classrooms in Athens, Greece, reported mean classroom UFP counts of 24 000 cm^{-3} (Diapouli et al., 2007). As automobile traffic is a known source of UFPs (Cyrys et al., 2003; Gidhagen et al., 2004; Geller et al., 2006) between-study differences in classroom UFP levels may be partially explained by differences in traffic density outside schools. Indeed, elemental carbon (a common component of UFPs) levels in schools have been shown to decrease with increasing distance from busy motorways (Janssen et al., 2001). However, differences in building construction might also contribute to between-study differences in classroom UFP levels as the present study and that of Fromme et al (2006) were conducted in colder climates in which tighter building

construction may lead to decreased infiltration of outdoor air relative to buildings constructed in warmer climates such as that of Athens, Greece.

Of the independent variables examined, only wind speed and outdoor UFPs were significant determinants of classroom UFP counts. However, little between-classroom variation in volume, temperature, and relative humidity might have prevented us from detecting the potential effects of these variables. Indeed, a positive relationship between indoor relative humidity and mean UFP counts has been reported previously for residential environments (Weichenthal et al., 2007b). However, this same study failed to detect a significant relationship between indoor temperature and volume and mean UFP counts in homes (Weichenthal et al., 2007b), and as such these variables may be of little importance in predicting classroom UFP levels.

A positive relationship was detected between window opening and classroom UFPs, and this is consistent with the observed association between outdoor UFP levels and classrooms UFP counts. However, the coefficient for this variable was not statistically significant perhaps owing to the small number of days in which classroom windows were open. While air exchange rate was not identified as a significant predictor of classroom UFP counts, measurement error for this variable might have prevented us from detecting such a relationship as it is known to bias the regression slope for miss-measured variables towards the null (Armstrong, 1998). Therefore, future studies should include more accurate estimates of air exchange rate in order to further evaluate the potential influence of this variable on classroom UFP levels. Other studies exploring determinants of classroom UFP counts were not identified, but a positive association between air exchange rates and fine particle levels has been reported previously for

residential environments (Abt et al., 2000) and a similar relationship seems likely for classroom UFPs, particularly in the absence of indoor UFP sources.

Outdoor temperature and wind speed were each identified as important predictors of outdoor UFP levels, and previous studies have also detected inverse relationships between temperature (Jeong et al., 2004; Jeong et al., 2006), wind speed (Levy et al., 2003; Zhu et al., 2002; Zhu et al., 2006) and outdoor UFP counts. Therefore, our results appear to be consistent with previous findings. Nevertheless, we cannot rule out the potential influence of unmeasured confounding factors on the observed associations between temperature, wind speed, and outdoor UFP counts.

In a two-week evaluation of model performance, model estimates for classroom UFP counts performed moderately well in the absence of strong indoor UFP sources. However, no correlation was observed between measured and predicted classroom UFP counts when data collected on days with active indoor UFP sources were included in the analysis. Differences between measured and predicted outdoor UFP counts were substantially larger than those for indoor levels. However, similar models might still be useful in population-based studies if quantitative data for outdoor UFP counts cannot be obtained by other more accurate means.

Medically relevant human exposure levels are currently poorly understood for UFPs, and as a result it remains difficult to assess how accurate model estimates need to be to be of use in population-based studies. As such, the observed differences between measured and predicted classroom UFP counts in this study may be small enough to support the use of similar models in future investigations. However, further research is

required to incorporate indoor source variables as well as variables for external traffic conditions into the models presented.

5. Conclusion

School-age children spend a large portion of their time in classrooms. As such, population-based studies interested in the health effects of airborne contaminants must account for exposures occurring in these locations in order to obtain an accurate depiction of children's overall exposure profiles. In a cross-sectional survey of classroom UFP levels during the winter months, wind speed and outdoor UFP counts were identified as significant determinants of classroom UFP levels. Predictive models based on outdoor UFP data alone performed reasonably well in estimating classroom UFP counts on days in which active indoor UFP sources were not present. However, no correlation was observed between measured and predicted values for classroom UFP counts when a strong indoor UFP source was present in schools. Therefore, while similar models may be useful in population-based studies interested in the potential health effects of UFP exposures, their application is likely limited to schools without significant indoor UFP sources. Future studies should aim to include schools with active indoor UFP sources in order to explore the effects of such sources on classroom UFP counts.

TABLES

Table 1 Summary statistics for indoor and outdoor measures at Schools A and B

Variable Measured	N_A/N_B	Location					
		School A			School B		
		Mean (SD)	Min	Max	Mean (SD)	Min	Max
UFPs $_{indoor}$ (cm^{-3})	30 / 30	5429 (3209)	1159	10 853	4605 (2239)	1033	11 414
Temp $_{indoor}$ (^{o}C)	28 / 29	20.8 (1.3)	19.0	23.7	22.0 (1.8)	18.6	25
RH $_{indoor}$ (%)	28 /29	25.8 (6.9)	14.0	41.2	17.0 (5.8)	9.8	34.1
CO_2 (p.p.m)	28 / 29	1558 (564)	784	2817	1011 (291)	543	1942
Ach (h^{-1})[a]	27 / 26	1.19 (0.74)	0.29	3	0.92 (0.75)	0.23	3.3
$PM_{2.5}$ ($\mu g/m^3$)[b]	13 / 14	22.6 (22.7)	4.9	78.7	10.9 (10)	4.28	40.8
UFPs $_{outdoor}$ (cm^{-3})[c]	30 / 30	14 877 (8512)	2590	29 850	13 137 (11 038)	3695	39 750
Temp $_{outdoor}$ (^{o}C)	30 / 30	-9.3 (8.0)	-21.2	7.9	-14.0 (6.0)	-21.3	-2.7
RH $_{outdoor}$ (%)	30 / 30	65.4 (15.6)	38.6	93.9	58.1 (16.6)	36.4	92.1
Wind speed (km/h)	30 / 30	11.8 (6.5)	3.3	25.0	14.4 (6.2)	7.6	33.0
Room Volume (m^3)	30 / 30	217.6 (33)	167	311	222.8 (55)	170	426

SD, Standard Deviation; RH, Relative Humidity; N_A/N_B, number of measures for Schools A and B; Temp, Temperature; Min, Minimum; Max, Maximum. [a] Estimated air exchange rate. [b] $PM_{2.5}$ measures were collected in the gymnasium at School A and in a hallway at School B. [c] Outdoor UFP counts reflect the average of two 2-minute samples collected in the morning and afternoon outside each school.

Table 2 Single-variable models for the relationship between classroom UFPs and indoor/outdoor measures[a]

Dependent Variable	Independent Variable	N	β	95% CI	R^2
Classroom UFPs (cm^{-3})	Temperature $_{outdoor}$ (K) [b]	60	294	(-740, 1329)	0.02
	RH $_{outdoor}$ (%) [b]	60	-143	(-597, 310)	0.03
	Wind speed (km/h) [b]	60	-1873	(-2920, -825) *	0.20
	Temperature $_{indoor}$ (K) [b]	57	39	(-4865, 4944)	0.03
	RH $_{indoor}$ (%) [b]	57	-752	(-1929, 425)	0.06
	Classroom Volume (m^3) [b]	60	17	(-143, 179)	0.02
	CO_2 (p.p.m) [c]	57	-319	(-2022, 1383)	0.04
	UFP $_{outdoor}$ (cm^{-3}) [d]	60	1550	(930, 2171) *	0.32
	Ach (h^{-1})	53	-2.3	(-1086, 1081)	0.03
	Windows Open	60	798	(-2112, 3709)	0.03

N, number of classroom measures; 95% CI , 95% Confidence Interval; RH, Relative Humidity.
[a] Models represent data from Schools A and B combined and all models included a dichotomous "school" parameter which had no statistical significance.
[b] Coefficient for 10 unit increase.
[c] Coefficient for a 1000 unit increase.
[d] Coefficient for a 10 000 unit increase.
* Relationship significant at 0.05 level.

Table 3 Single-variable models for the association between outdoor UFPs and ambient weather conditions

Dependent Variable	Independent Variable	N	β	95% CI	R^2
Outdoor UFPs (cm^{-3})	Temperature $_{outdoor}$ (K) [b]	60	-3604	(-7174, -33)*	0.07
	RH $_{outdoor}$ (%) [b]	60	-257	(-1877, 1361)	0.00
	Wind speed (km/h) [b]	60	-8758	(-12 172, -5344)*	0.32

N, number of classroom measures; 95% CI , 95% Confidence Interval; RH, Relative Humidity.
[a] Models represent data from Schools A and B combined and all models included a dichotomous "school" parameter which had no statistical significance.
[b] Coefficient for 10 unit increase.
* Relationship significant at 0.05 level.
Table 4 Predictive models for classroom UFP counts and outdoor UFP counts

Table 4 Predictive models for classroom UFP counts and outdoor UFP counts

Dependent Variable	α	95% CI	Independent Variable	β	95% CI
Indoor model					
$UFPs_{indoor}$ (cm^{-3})	3228 cm^{-3}	(2199, 4257)	$UFPs_{outdoor}$ (cm^{-3})	0.149	(0.089, 0.21)
Outdoor model					
$UFPs_{outdoor}$ (cm^{-3})	109 682 cm^{-3}	(49 047, 170 316)	$Temp_{outdoor}$ (K)	-308	(-538,-78)
			Wind speed (km/h)	-1015	(-1282, -748)
			Temp_c*Wind speed_c	137	(79, 195)

Table 5 Summary of observed and predicted classroom UFP levels

School	Observed UFP count [a]		Predicted UFP count [a]		Difference [b]	
	Mean (cm^{-3})	95% CI	Mean (cm^{-3})	95% CI	Mean (cm^{-3})	95% CI
School C						
Indoor [c]	2942	(2139, 3744)	3852	(3680, 4024)	-910	(-1655, -166)
Outdoor [d]	4193	(3039, 5347)	15 315	(12 198, 18 433)	-11 122	(-14 137, -8107)
School D						
Indoor [c]	7147	(3108, 11 187)	3918	(3617, 4220)	3228	(-445, 6902)
Outdoor [d]	4670	(2649, 6691)	15 251	(11 980, 18521)	-10 580	(-14 068, -7093)

[a] The models developed in Schools A and B were used to estimated indoor and outdoor UFPs at Schools C and D for eight days each.
[b] Difference = Observed – Predicted.
[c] Predictions generated using the indoor model in Table 4.
[d] Predictions generated using the outdoor model in Table 4.

FIGURES

Figure 1. Scatter-plot of classroom UFP counts and wind speed.

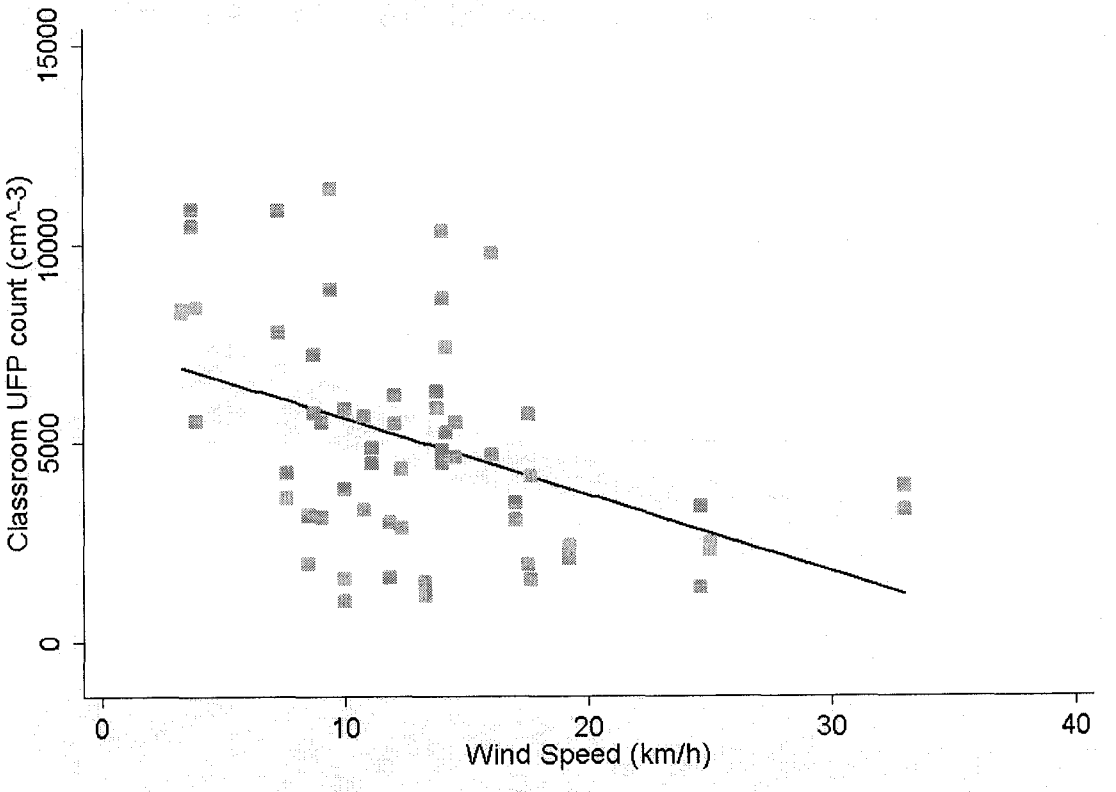


Figure 2. Scatter-plot of classroom UFP counts and outdoor UFP counts.

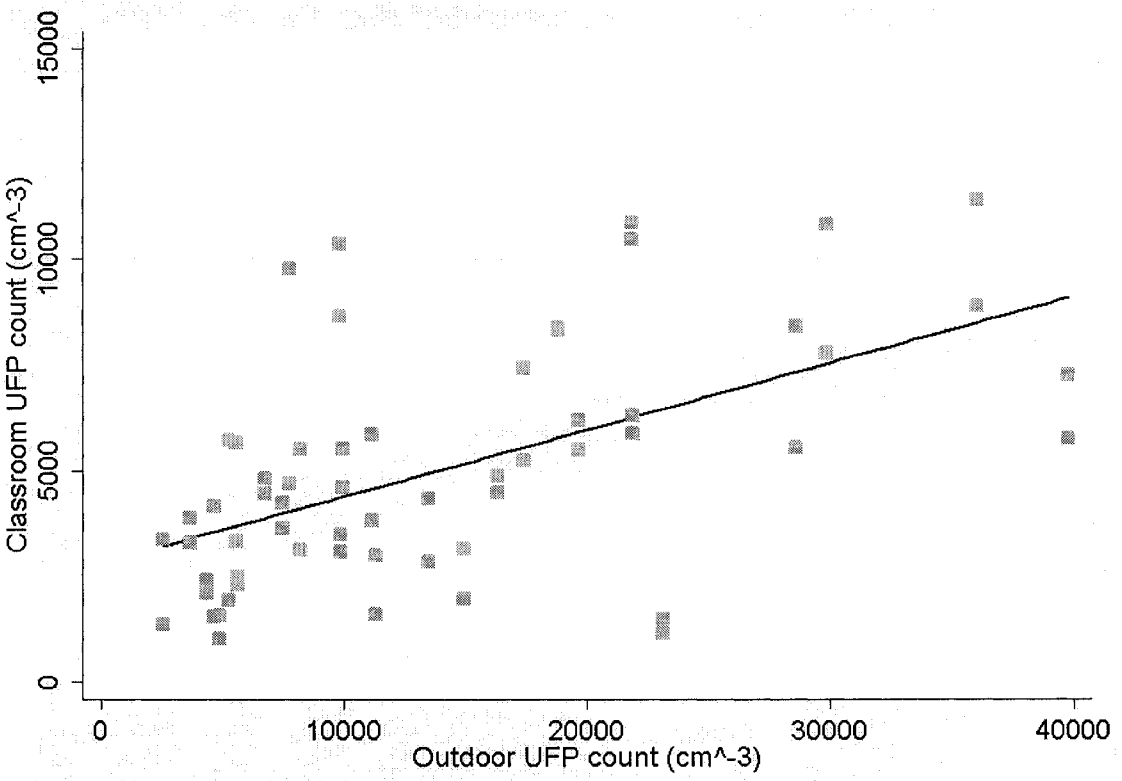


Figure 3. Real-time plot of classroom UFPs in school A. Peaks represent time-periods in which students enter/exit the school.

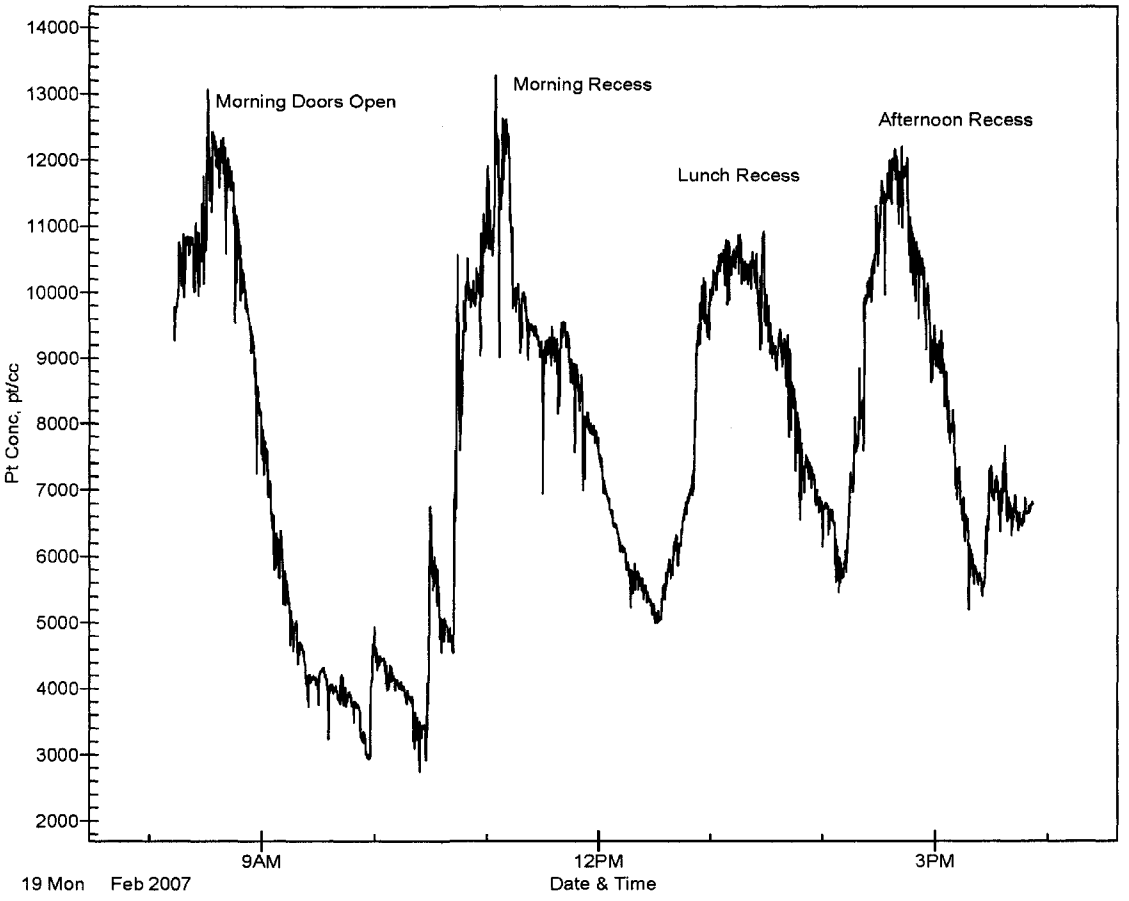


Figure 4. Scatter-plot of outdoor UFP counts and wind speed.

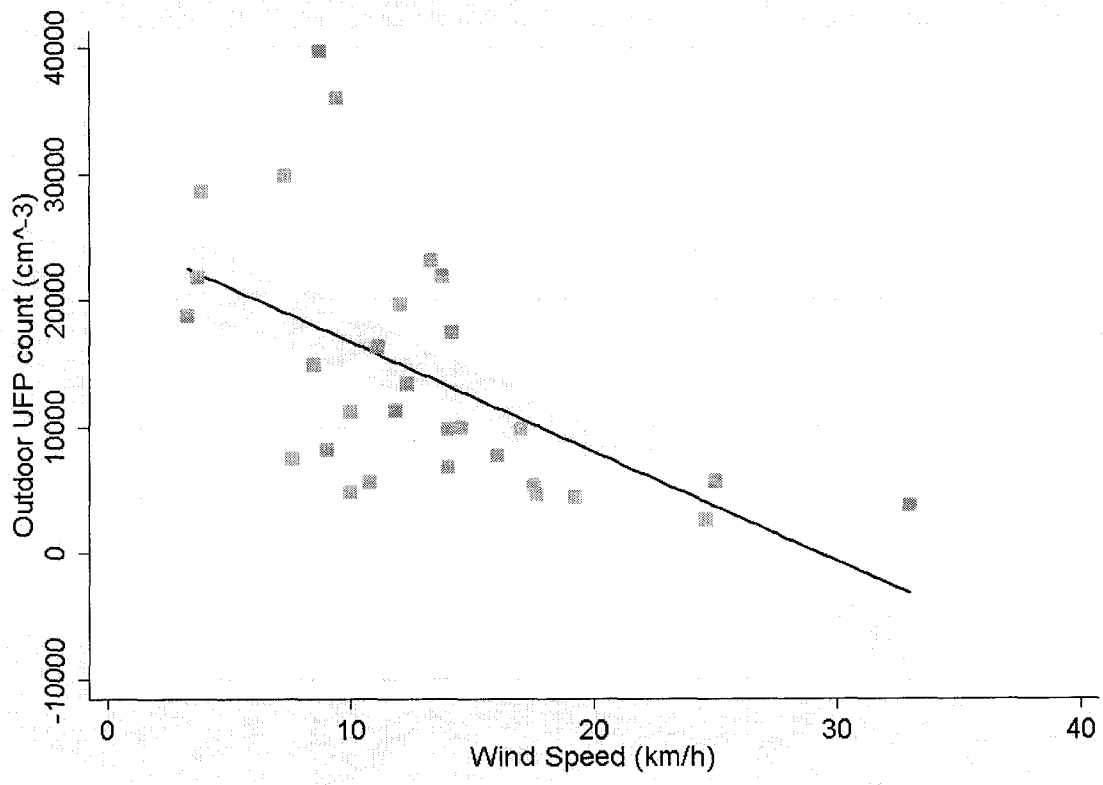


Figure 5. Scatter-plot of outdoor UFP counts and outdoor temperature.

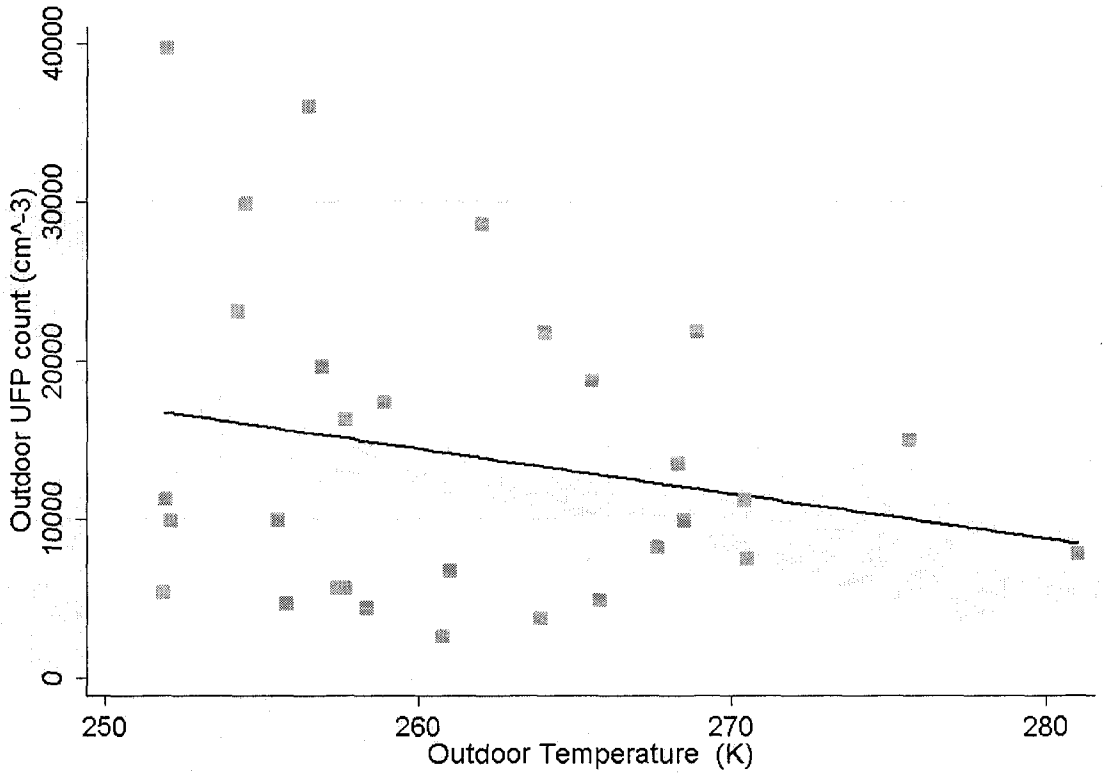


Figure 6. Correlation between measured and predicted classroom UFP counts.

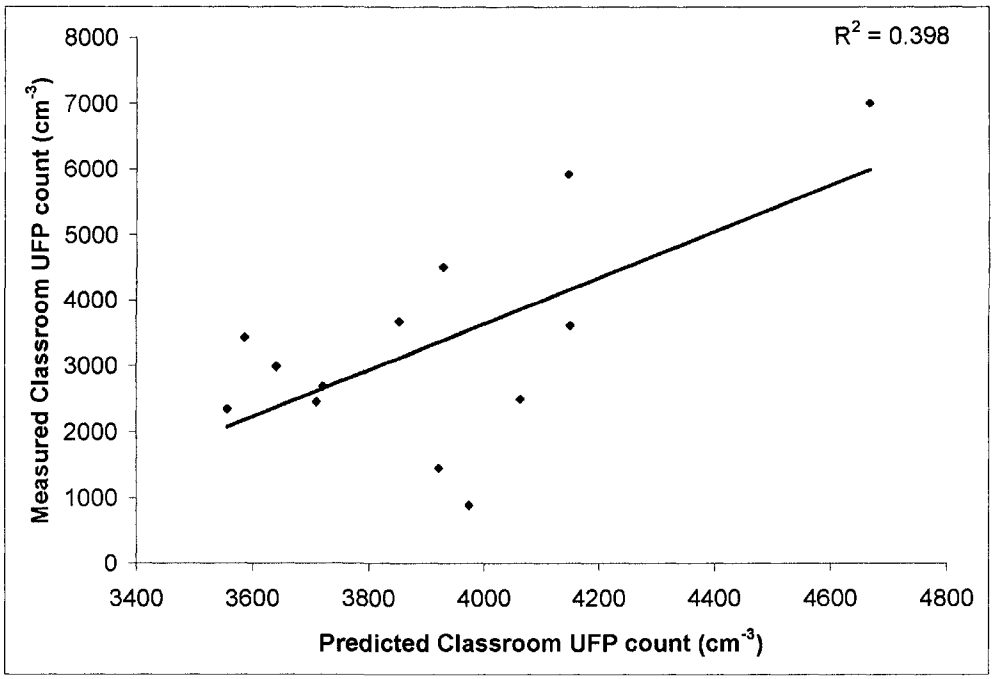
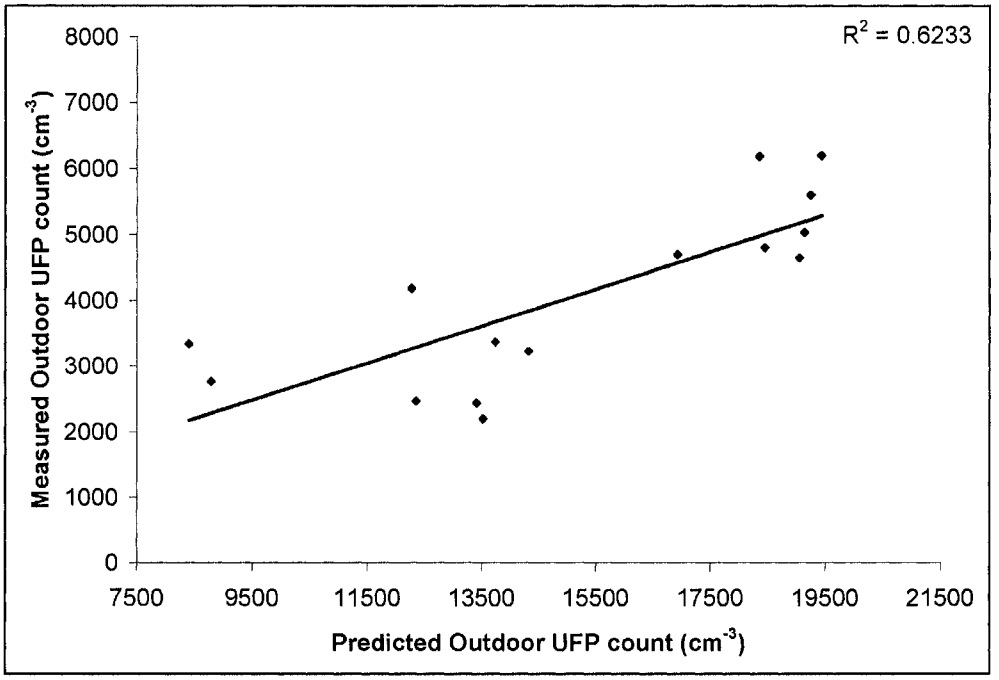


Figure 7. Correlation between measured and predicted outdoor UFP counts.



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6. DISCUSSION

Exposure assessment remains a challenge in population-based studies owing to logistical and financial constraints which prevent the collection of detailed exposure information for large numbers of study participants (Nieuwenhuijsen et al., 2006). For UFPs specifically, exposure assessment depends on expensive monitoring devices not practically applicable in population-based studies. In addition, alternatives such as fixed-site ambient monitoring are not ideal because central-site measures may not reflect actual exposures owing to time spent indoors and/or spatial variation within a given region (Wallace and Howard-Reed, 2002; Hussein et al., 2005; Tuch et al., 2006). Therefore, studies interested in the potential health effects of UFP exposures may need to rely on exposure modeling to estimate exposures for large numbers of study participants.

Regression methods have been used to construct predictive models for airborne bacteria and fungal concentrations in schools (Bartlett et al., 2004a; Bartlett et al., 2004b), and to describe the contribution of children's activities to dermal pesticide exposures following residential pesticide application (Freeman et al., 2005). For ambient air pollution, land use regression (LUR) methods are available which seek to predict pollutant concentrations based on surrounding land use (e.g. commercial, industrial, residential) and traffic characteristics as well as fixed-site monitoring data (Jerrett et al., 2005). However, while LUR methods may be useful for estimating outdoor pollutant levels within a given region, they depend on a dense network of monitoring stations and models developed in one geographic location are not easily applied to other areas (Jerrett et al., 2005). Furthermore, LUR models provide estimates of ambient air pollutant concentrations which might not represent actual participant exposures owing to time spent indoors. Therefore, population-based studies requiring estimates of personal exposure may be

more likely to rely on exposure models developed for specific environments using detailed indoor/outdoor measures from a random sub-set of study participants along with information on expected determinants of exposure (Gilliland et al., 2005). Once developed, these models can then be applied to estimate exposures for large numbers of study participants using time-activity data and determinant information collected from subjects using a questionnaire or other sources such as public databases. Ideally, information for determinant variables should be available at minimal expense; otherwise the application of such models may no longer be cost-effective.

In this study, we explored the applicability of such an approach in estimating UFP exposures in homes, schools, and transportation environments because children spend the majority of their time in these locations. As a secondary objective, our goal was to perform small-scale evaluations of these models to determine which environments may be most suitable for exposure modeling in future studies. Presented next is a discussion of model performance and application, as well as the potential influence of measurement error on model coefficients.

6.1 MODEL PERFORMANCE

Studies were conducted to characterize UFP exposures in homes, schools, and transportation environments and to develop models to predict such exposures based on readily available information. The main findings of these investigations are summarized below with respect to model performance in each environment.

Homes

- On average, model predictions for UFP exposures in homes underestimated observed values by 944 cm^{-3} (95% CI: -9247, 11 136). A low correlation was detected between observed and predicted UFP levels in homes (r = 0.28), but the strength of this relationship improved substantially with the removal of three outlying data points which exceeded a difference of 10 000 cm^{-3} (r = 0.54).
- Final Predictive Model:

$$\mathbf{UFP_{HOMES} = -20\,440 + 9757(\mathit{Oven}) + 13\,770\,(\mathit{Smoking}) + 865.5(\mathit{RH}) - 2.95(\mathit{Volume})}$$

UFP_{HOMES}: Mean UFP level in homes (cm^{-3})

Smoking: Indoor cigarette smoking (Yes/No)

RH: Indoor relative humidity (%)

Oven: Electric oven use (Yes/No)

Volume: Home volume (m^3)

Transportation Environments

- Model performance was not evaluated on a different *walking route* because outdoor temperatures during data collection for model evaluation were generally below the minimum recommended operating temperature for the P-TRAK (below $0^{o}C$), the instrument used to monitor UFPs.
- A moderate correlation ($r = 0.50$) was observed between measured and predicted *automobile UFP exposures*, with model estimates on average underestimating measured values by 3540 cm^{-3} (95% CI: -7190, 14 271). This correlation increased ($r = 0.77$) with the removal of two outlying values for which no clear cause was noted.
- The correlation between measured and predicted *bus exposures* was comparable to that observed for the automobile ($r = 0.55$), with model estimates on average overestimating measured values by 6289 cm^{-3} (95% CI: 761, 11 818). This correlation improved ($r = 0.65$) with the removal of two outlying values, one of which was collected on a morning in which the public transit bus traveled directly behind a school bus. No clear cause was apparent for the second outlying data point.

❖ Final Predictive Models:

$$\mathbf{UFP_{WALK} = 294\,051 + 2169(\mathit{Morning}) - 932(\mathit{Temp}) - 404(\mathit{Wind}) + 58(\mathit{Temp\_c}*\mathit{Wind\_c})}$$

$$\mathbf{UFP_{BUS} = 184\,900 - 525(\mathit{Temp}) - 519(\mathit{Wind})}$$

$$\mathbf{UFP_{AUTO} = 275\,979 - 805(\mathit{Temp}) - 575(\mathit{Wind}) + 19(\mathit{Temp\_c}*\mathit{Wind\_c})}$$

$UFP_{WALK/BUS/AUTO}$: Mean UFP level in each environment (cm^{-3})

Morning: Morning time-period (Yes/No)

Temp: Ambient temperature (K)

Wind: Wind speed (km/h)

*Temp_c*Wind_c*: Temperature-wind speed interaction term using centered variables (K·km/h)

Note: Centered variables were generated by subtracting the mean temperature/wind speed over all days from the value measured on each individual transit day. This relationship is depicted below:

$Temp\_c = Temp - 288.71\text{K}$

$Wind\_c = Wind - 14.93$ km/h

Example: At a wind speed of 10 km/h, a 10°C increase in temperature corresponds to a decrease of 9922 cm^{-3} for UFPs in the automobile.

Schools

- On average, model estimates overestimated *classroom UFP counts* at School C by 910 cm^{-3} (95% CI: 166, 1655) and underestimated *classroom UFP counts* at School D by 3228 cm^{-3} (95% CI: -445, 6902).
- For both schools combined, a substantial correlation (r = 0.63) was observed between measured and predicted *classroom UFP counts* after the removal of three outlying data points collected in School D on days in which an indoor UFP source was active. When these points were kept no correlation was observed between measured and predicted classroom UFP counts (r = 0.0).
- On average, model estimates for *outdoor UFP counts* overestimated values at School C by 11 122 cm^{-3} (95% CI: 8107, 14 137) and by 10 580 cm^{-3} (95% CI: 7093, 14 068) at School D. A substantial correlation (r = 0.63) was observed for measured and predicted *outdoor UFP counts* for both schools combined, and this correlation increased with the removal of one outlying data point for which no clear cause was identified (r = 0.79).

❖ Final Predictive Models:

$$\mathbf{UFP_{CLASSROOM} = 3228 + 0.149(\textit{Outdoor UFP})}$$

$$\mathbf{UFP_{OUTDOOR} = 109\ 682 - 308(\textit{Temp}) - 1015(\textit{Wind}) + 137(\textit{Temp\_c}*\textit{Wind\_c})}$$

$UFP_{CLASSROOM}$: Mean UFP level in classroom (cm^{-3})

$UFP_{OUTDOOR}$ = Mean ambient UFP level outside classroom (cm^{-3})

Temp: Ambient temperature (K)

Wind: Wind speed (km/h)

*Temp_c*Wind_c*: Temperature-wind speed interaction term using centered variables (K·km/h)

Note: Centered va riables were generated by subtracting the mean temperature/wind speed over all days from the values determined on each sampling day. This relationship is depicted below:

$Temp\_c = Temp - 261.92$ K

$Wind\_c = Wind - 13.09$ km/h

Example: At 10 km/h, a 10°C increase in temperature corresponds to a decrease of 7312 cm^{-3} for outdoor UFPs.

In small-scale evaluations of model performance, correlations between measured and predicted values were greatest for UFP exposures in buses and the automobile followed by those in classrooms and homes. However, local UFP sources such as electric kitchen stoves in schools and large diesel vehicles in transportation environments had negative effects on model performance. In general, predictive models tended to *overestimate* UFP levels in buses, classrooms at School C, and outdoor UFP levels at Schools C and D. Alternatively, model estimates tended to *underestimate* UFP levels in homes, the automobile, and classrooms at School D. Overestimation of UFP levels in buses may owe in part to higher traffic counts on the model development route (~ 2000 vehicles/hour) relative to the route used for model evaluation (~ 1000 vehicles/hour). Indeed, traffic counts on model development and evaluation routes were approximately equal for the automobile and the observed difference between measured and predicted values was approximately half that observed for buses. Regardless, future studies should include "traffic count" variables in predictive models for automobiles and buses in order to account for traffic variation between transit routes. In addition, future studies should include variables for in-school UFP sources as classroom predictions for School D likely underestimated observed values owing to the presence of an electric kitchen stove which was not accounted for in the school model presented above. Similar sources were not identified in School C, and while model predictions slightly overestimated observed values, the observed difference between measured an predicted UFP levels at School C was approximately one-third that observed for School D. Reasons for the overestimation of outdoor UFP levels at Schools C and D are less apparent, but may owe in part to seasonal differences between model development and evaluation periods. Specifically, ambient temperatures were much colder during model development (mean School A/B = -9.3 $^{\circ}$C/-14.0°C) relative to model evaluation (mean = 2.9°C)

and only three days during model development had temperatures comparable to those recorded during model evaluation. Therefore, overestimation of outdoor UFPs at Schools C and D may owe in part to extrapolation beyond the range of ambient temperatures present during model development. Indeed, as the degree of overestimation was essentially equal for both schools other factors such as changes in traffic counts and/or other ambient UFP sources seem less likely. Ideally, data collection for model evaluation and model development would have taken place concurrently, but this was not possible owing to the limited number of instruments available. In homes, measured and predicted UFP levels differed on average by fewer than 1000 cm^{-3}. However, the correlation between measured and predicted UFP levels in homes was less than those observed for classrooms and transportation environments and this may owe in part to unidentified UFP sources in residential environments (Li et al., 1993; Abt et al., 2000; Wallace, 2000; Dennekamp et al., 2001; Wallace and Howard-Reed, 2002; Morawska et al., 2003; He et al., 2004; Wallace et al., 2004; Afshari et al., 2005; Hussein et al., 2005; Matson, 2005; Wallace, 2005). Collectively, our findings suggest that UFP exposure modeling may be more suitable for transportation environments and classrooms relative to homes, particularly in the absence of local UFP sources. However, further research is required to examine whether similar models may provide better estimates of UFP levels in homes over several days relative to the short 16-hour time-period explored in the current investigation.

All model predictions over or underestimated observed UFP levels to some extent. However, with the exception of the outdoor UFP model for Schools C and D, the amount of bias (the difference between measured and predicted values) observed was small relative to the absolute value for UFP levels in each environment. Specifically, for homes, schools, and transportation environments our findings indicate that in the worst-case scenario the average

difference between measured and predicted values was approximately 6000 cm^{-3}, with an upper 95% confidence interval of approximately 14 000 cm^{-3}. Therefore, this difference may be small enough to support the use of similar models in future studies as meaningful changes in health status are not expected for fluctuations within this range. At the very least, similar models may be useful in classifying subjects into categories of exposure such as greater than or less than 100 000 cm^{-3}. Indeed, this cut-off value may be a reasonable starting point as significant vasoconstriction has been observed in healthy adults exposed to UFPs in this concentration range relative to subjects exposed to levels of approximately 5000 cm^{-3} (Rundell et al., 2007). However, exposure measurement error will likely have an impact on future studies exploring the potential health effects of UFP exposures and this issue is now addressed.

6.2 MEASUREMENT ERROR IN MODEL DEVELOPMENT AND APPLICATION

Measurement Error in Model Development

In this investigation, the dependent variable of each model was a continuous measure of UFP exposure and was determined using a TSI P-TRAK in each environment. Previous studies have explored the accuracy of the P-TRAK relative to more sophisticated monitoring devices, and between-instrument correlations ranging from 0.8 to 0.99 have been reported with higher correlations generally observed for indoor environments relative to outdoors (Matson et al., 2004; Zhu et al., 2006b). Therefore, the dependent variable in each model was almost certainly influenced by measurement error as the P-TRAK is known to produce imperfect estimates of exposure. Assuming that P-TRAK measures were randomly distributed about true values, the impact of this error was likely a loss of precision in model coefficients (increased 95% confidence interval width) because measurement error in the dependent variable does not alter the regression slope but leads to increased uncertainty regarding the true relationship between explanatory and outcome variables (Armstrong et al., 1992; Gustafson, 2004). This effect could be reduced through the application of more sophisticated monitoring devices such as scanning mobility particle sizers (SMPS) or more accurate condensation particle counters. However, such devices cost considerably more than the P-TRAK and in the case of SMPS may not be as easily transported.

For continuous determinant variables, measurement error is assumed to be non-differential meaning that the error associated with each variable was not correlated with the value observed for UFP levels in each environment. For example, in the home model we assume that measurement error for relative humidity was not greater (or smaller) at increased UFP levels and vice versa. Measurement error is also assumed to be additive for continuous explanatory

variables meaning that measurement error was not proportional to the actual value of the predictor. For example, we have no reason to believe that measurement error for relative humidity in the home model depended on the actual value for relative humidity in the home. For dichotomous explanatory variables in the home model, measurement error is also assumed to be non-differential meaning that the sensitivity and specificity of exposure assessment did not depend on UFP levels in homes. Under these assumptions, measurement error in continuous and dichotomous explanatory variables is known to attenuate regression coefficients for models with single predictor variables (Armstrong et al., 1992; Gustafson, 2004). When multiple predictors are present in the same model, the effect of measurement error on model coefficients may not be attenuation if explanatory variables are highly correlated (Gustafson, 2004). However, this was not the case for explanatory variables included in the models presented in this study ($0.0 < |r_s| < 0.39$), and while these correlations may themselves be affected by measurement error, the overall impact of measurement error for determinant variables was likely attenuation of model coefficients. Specifically, the coefficient for outdoor UFPs in the school model likely underestimates the impact of ambient UFPs on classroom levels owing to error in P-TRAK measures. Similarly, the coefficient for volume in the home UFP model likely underestimates the impact of this variable on residential UFP exposures as home volumes were not determined quantitatively but were estimated based on home dimensions and an assumed ceiling height of 2.4 meters. Likewise, measurement error likely limited our ability to detect a significant relationship between air exchange rates and UFP levels in homes and classrooms as this variable was not determined quantitatively but was estimated using indoor carbon dioxide measures. Significant attenuation of the coefficient for relative humidity in the home model seems unlikely, however, as this variable was measured with a reported accuracy of ± 3%. Similarly, while

spatial variation in ambient temperature might have contributed to measurement error for this variable, a dramatic difference between fixed-site measures and temperature values outside schools and transportation environments seems unlikely. On the other hand, error associated with wind speed measures may be more pronounced as high rise buildings in urban areas have been shown to increase wind speeds in their vicinity (Murakami et al., 1979). As a result, "true" wind speeds along the transit route might have differed from fixed-site measures, which were collected away from high-rise buildings. In this case, attenuation of wind speed coefficients was likely more pronounced for bus and automobile models as the walking route and schools were located away from high rise buildings. While real-time personal monitors could be employed to reduce potential measurement error resulting from the use of fixed-site measures for ambient temperature and wind speed, this approach may not be suitable for large-scale investigations given the increased cost of collecting such data relative to historical weather databases. We cannot rule out measurement error in dichotomous predictor variables included in final models (electric oven use and smoking), but a large amount of attenuation seems unlikely as the presence or absence of these predictors was generally verified in homes during each sampling period.

Measurement Error in Model Application

When applying the models presented, measurement error in model predictions is expected to be non-differential meaning that error in UFP estimates would not depend on a subjects' disease status. In this case, bias in UFP exposure estimates (i.e. a difference between predicted and "true" values) would not modify the observed association between exposure and outcome because exposure distributions for diseased and non-diseased cohorts would not be shifted relative to each other (Armstrong et al., 1992). However, the lack of precision in model

estimates would tend to widen the distributions of UFP exposures for each cohort leading to more overlap and less distinction between UFP exposures among diseased and non-diseased subjects (Armstrong et al., 1992). The overall impact is an attenuation of the observed relationship between exposure and disease (e.g. odds ratio), with the amount of attenuation depending on the precision with which exposure is measured.

6.3 MODEL APPLICATION

Investigators are unlikely to examine the separate effects UFP exposures in homes, schools, and transportation environments. Alternatively, the models presented or similar models may be used in conjunction with time-activity data to estimate cumulative exposure values using all three models combined. However, the process of model development within a random sub-set of participants may need to be repeated for each study location as models developed in one geographic area may not reflect exposures in other regions owing to differences in traffic characteristics, building construction, or other potentially important variables. The generalizability of the models presented could be increased, however, by incorporating such factors as model determinants.

While data for determinants such as temperature, wind speed, home volume, cigarette smoking, and electric oven use can be obtained easily once models have been developed, information for determinants such as indoor relative humidity may not be readily available for large numbers of homes. In this case, probabilistic techniques such as direct simulation may be used to generate values for indoor relative humidity and thus allow researchers to estimate in-home UFP levels in the absence of quantitative measures. In this type of analysis, model input parameters are specified as probability distributions instead of single values and the model is run many times to obtain a distribution of plausible exposure estimates (Paustenbach, 2000). For the specific case of applying our in-home UFP exposure model in the absence of quantitative relative humidity data, coefficients for known determinants would be placed in the model as constants and a distribution would be assigned only to indoor relative humidity. In general, probability distributions for determinants that are not easily assessed through a questionnaire or public databases could be based on a combination of subset measures and literature values.

In general, our findings are encouraging in that information for the majority of determinants identified can be obtained easily at minimal expense once a model is developed. For example, hourly temperature and wind speed data are available online from public data bases (e.g. Environment Canada), and information on electric oven use, indoor cigarette smoking, and home volume can be collected using a reliable questionnaire. The ability of temperature and wind speed data to predict UFP levels in bus and automobile environments is particularly encouraging as historical weather data is readily available, thus facilitating the use of similar models to estimate retrospective UFP exposures. While classroom UFPs were predicted only by outdoor levels, our findings suggest that outdoor temperature and wind speed data may be used to estimate UFP levels outside schools in the absence of quantitative measures. As a result, studies interested in UFP exposures in schools could develop two models: one to predict classroom UFPs based on outdoor levels, and one to predict outdoor UFPs based on temperature and wind speed. Together, these two models could then be applied to obtain an estimate of UFP levels in classrooms. Again, however, the presence of UFP sources in schools should be investigated in order to incorporate these factors into the model.

In developing models similar to those presented, the size of the sub-sample required is likely to remain an issue and in most cases will be determined by the resources available. In this study, 36 home, 60 classroom, and 160 transportation measures were collected to develop the models presented above. For homes in particular, sample size limitations likely prevented us from detecting a significant effect for heating systems and resulted in large 95% confidence interval widths for the effects of electric oven use and indoor cigarette smoking. For example, using the fact that standard errors are proportional to $1/\sqrt{n}$, a sample size of approximately 110 homes would be required to obtain a 95% confidence interval width of 10 000 cm^{-3} for electric

oven use, and approximately 300 homes would be required for the coefficients for home heating systems to reach statistical significance. Coefficients for determinant variables in classroom and transportation models were estimated fairly precisely, however, and similar sample sizes may be appropriate for future investigations.

When applying models similar to those presented, potential confounding by other indoor air pollutants must be considered. For example, suspected respiratory irritants such as nitrogen dioxide and respirable particulate matter may be correlated with UFP levels in homes (Dennekamp et al., 2001; Seaton and Dennekamp, 2003; Weichenthal et al., 2007b) and thus may confound an observed association between UFPs and asthma. Confounding by indoor nitrogen dioxide may be reduced by excluding subjects in homes with natural gas appliances, but it may be difficult to separate the independent effects of UFPs and respirable particulate matter as our findings suggest that indoor UFPs and PM_4 are highly correlated ($r = 0.73$). In addition, when applying models similar to those presented, non-differential measurement error will likely attenuate the observed association between UFP exposure and health outcome assuming that exposure measurement error is similar for diseased and non-diseased cohorts. Therefore, preliminary studies employing UFP exposure assessment models should interpret their findings with caution. In fact, as little research has focused on the potential health effects of UFP exposures in common environments, it may be worthwhile for preliminary studies to employ quantitative exposure measures in order to increase the likelihood of detecting a significant relationship between UFP exposure and the health outcome of interest. In particular, quantitative measures for UFP levels in homes may be most important as our findings suggest that predicting such exposures may be difficult. Under this approach, models for transportation and school

environments could be applied to supplement quantitative home data to account for UFP exposures in these environments.

7. CONCLUSIONS

Exposure to airborne particulate matter has a negative effect on respiratory health in both children and adults, and the ultrafine fraction of particulate air pollution is of particular concern owing to its increased ability to cause oxidative stress and inflammation in the lungs. In this investigation, our objective was to characterize UFP exposures in homes, schools, and transportation environments and to develop models to predict such exposures. A number of important determinants were identified including ambient temperature and wind speed for transportation environments, outdoor UFPs for classrooms, and electric oven use, cigarette smoking, indoor relative humidity, and volume for homes. In general, our findings suggest that classrooms and transportation environments may be more suitable for UFP exposure modeling than homes. However, further research is required to evaluate the longitudinal performance of the home UFP exposure model presented in the current investigation. In addition, variables such as vehicle ventilation, traffic counts/characteristics, and in-school UFP sources should be incorporated into future models as these factors may improve the predictive performance of the models presented. Nevertheless, our findings are encouraging in that we demonstrate for the first time the possibility of obtaining UFP exposure estimates for homes, schools, and transportation environments using models based on ambient weather data and other readily available information. As such, similar models may be useful in population-based studies interested in the potential health effects of UFP exposures.

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APPENDICES

APPENDIX 1. MANUSCRIPT E

INDOOR NITROGEN DIOXIDE AND VOC EXPOSURES: SUMMARY OF EVIDENCE FOR AN ASSOCIATION WITH CHILDHOOD ASTHMA AND A CASE FOR THE INCLUSION OF INDOOR ULTRAFINE PARTICLE MEASURES IN FUTURE STUDIES

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Abstract

Childhood asthma is a complex disease having both genetic and environmental risk factors. As such, it is important to identify indoor exposures that may contribute to asthma symptoms in order to minimize the likelihood of disease onset or exacerbation. Here we summarize epidemiological evidence regarding the potential relationship between indoor nitrogen dioxide, volatile organic compounds (VOCs), and childhood asthma. In general, VOC exposure studies have been more consistent in demonstrating a significant relationship with asthma or related symptoms, and studies of indoor nitrogen dioxide exposure are limited in that most do not control for indoor VOC exposures. Therefore, when possible future studies should include both types of exposure measures as well as those for other potential risk factors such as ultrafine particles which have been shown to contribute to airway inflammation.

Introduction

Childhood asthma is increasingly prevalent [1], and the resulting social, medial, and financial burdens of this disease make it a growing public health concern world wide. A number of indoor environmental risk factors for childhood asthma have been described to date and include both biological and chemical contaminants. The biological risk factors for childhood asthma have been reviewed elsewhere [2, 3], and while indoor dust mite, cockroach, and cat allergens are known triggers of allergic asthma in some individuals, evidence is less conclusive for non-biological indoor pollutants such as nitrogen dioxide, volatile organic compounds (VOCs), and ultrafine particles (UFPs).

Indoor sources of VOCs include paints, sealants, adhesives, pressed wood products, deodorizers, and furnishings [4], whereas nitrogen dioxide is produced indoors mainly by combustion sources such as natural gas kitchen stoves with minor contributions from tobacco smoke, fireplaces, and automobile exhaust from an attached garage [5]. Ultrafine particles are often produced by the same indoor sources as nitrogen dioxide, but are also produced by sources not associated with nitrogen dioxide such as electric kitchen stoves [6, 7]. While little attention has focused on the potential relationship between indoor UFP exposures and childhood asthma [27], several epidemiological investigations have explored the potential respiratory effects of indoor nitrogen dioxide and VOC exposures. Here we review studies employing quantitative exposure measures in an effort to summarize current evidence regarding the relationship between indoor nitrogen dioxide, VOCs, and childhood asthma. In doing so, we recognize the fact that a number of investigations have employed qualitative measures of indoor nitrogen dioxide (e.g. gas cooking) and VOC exposure (e.g. recent painting) and that several have detected a significant relationship with asthma, respiratory symptoms, and/or reduced lung function in

children [8-20]. However, findings from these studies remain difficult to interpret because proxy measures of exposure are not necessarily associated with actual indoor levels of nitrogen dioxide or VOCs. As such, studies employing qualitative measures have been excluded from this review and we focus only on those studies with quantitative exposure measures. To conclude, we provide a brief summary of evidence in support of a relationship between indoor UFPs and asthma, and support the inclusion of UFP exposure measures in future epidemiological investigations interested in indoor risk factors for this disease.

Methods

Studies were included in this review if they were published in English, did not appear in one of two previous reviews [4, 5], and employed quantitative measures to examine the relationship between indoor nitrogen dioxide or VOC exposure and childhood asthma or related symptoms. Articles were identified by systematically searching the Medline/Pubmed database, and using key words such as childhood asthma, respiratory illness, indoor exposures, nitrogen dioxide, and volatile organic compounds. Additional articles were also identified from the reference lists of publications retrieved by the above procedure.

Results

Epidemiological studies of indoor VOC exposure and childhood asthma

A number of epidemiological investigations have focused the potential relationship between indoor VOCs and childhood respiratory illness, and several have been reviewed previously [4]. These studies are summarized in Table 1 along with 4 additional studies which were not included in the previous review [21-26].

A cross-sectional survey was conducted in Sweden to study the prevalence of current asthma among secondary school children [21]. Participants completed a self-administered questionnaire and occupational hygienists inspected schools and noted details of building construction, materials, ventilation, and signs of dampness. In each of the 28 classrooms examined, hygienists also measured formaldehyde, nitrogen dioxide, air exchange rate, carbon dioxide, temperature, humidity, total VOCs, moulds, and bacteria in air. In addition, levels of endotoxin and cat, dog, and mite allergen were determined in settled dust. After controlling for atopy, food allergy, and day-care attendance, levels of formaldehyde and total VOCs, were significantly related to current asthma. However, stronger associations were observed for cat allergen, viable moulds, viable bacteria, and relative humidity. A significant inverse relationship was observed between room temperature and current asthma, but current asthma was not associated with exposure to nitrogen dioxide.

An Australian study used passive samplers to measure indoor formaldehyde in the living rooms, kitchens, and bedrooms of 80 volunteer homes [22]. A validated questionnaire was used to collect information on the frequency of childhood respiratory symptoms and atopy was assessed by skin prick tests for 12 common environmental allergens. An association was detected between bedroom formaldehyde and atopy, and more severe allergic sensitization was observed

with increasing formaldehyde exposure. No significant increase in the risk of asthma or respiratory symptoms was detected with formaldehyde exposure after adjusting for parental allergy or asthma, but among children with respiratory symptoms, symptoms were more frequent in those exposed to higher formaldehyde levels. The effects of indoor nitrogen dioxide, passive smoking, pets, fungal spores, and dust mite allergen levels were explored but did not significantly influence model estimates.

In a case-control study Rumchev et al examined the relationship between domestic VOC exposures and childhood asthma [23]. Cases were children discharged from a hospital emergency department in Perth, Australia, with asthma as the primary diagnosis. Controls were recruited from the community and were children of the same age group without doctor diagnosed asthma. A standardized questionnaire was used to gather information on child respiratory health, and all odds ratios were adjusted for levels of indoor air pollutants such house dust mite allergen, relative humidity, and temperature as well as factors such as atopy, family history of asthma, age, sex, smoking, socioeconomic status, and gas appliance use. VOCs were measured in summer and winter for 8 hours in the living room, and significantly increased risks of childhood asthma were observed with exposure to total VOCs, benzene, toluene, ethylbenzene, m-xylene, and dichlorobenzene. Exposure to total VOCs was still a significant risk factor for childhood asthma when formaldehyde was included in the model. However, when controlling for indoor nitrogen dioxide exposures the use of quantitative measures would have been preferred to qualitative data on exposure to gas heating or cooking.

A case-control study was conducted in Britain to examine the effect of indoor VOCs on the risk and severity of wheezing illness in children [24]. Cases and controls were children in primary school who participated in a previous study of traffic exposure and childhood wheezing

in 1995-1996. Surface wall moisture was measured in living rooms, kitchens, and children's bedrooms, and nitrogen dioxide and total VOCs were measured in kitchens and children's bedrooms respectively over a 4-week period. Formaldehyde was measured in children's bedrooms for 3-days using a diffusion sampling badge. A computerized questionnaire was used to gather information concerning smoking in the home, pets, and child drug treatment for asthma. Final odds ratios were adjusted for age, sex and socioeconomic status. Indoor dampness was observed to increase both the risk and severity of childhood wheezing illness, and among cases a significantly increased risk of night-time wheeze was observed for the highest quartile of formaldehyde exposure. However, no effect was observed for total VOCs or nitrogen dioxide on risk or severity of childhood wheezing illness. Therefore, this study supports a role for formaldehyde as a trigger of respiratory symptoms among children with persistent wheezing, but suggests that VOC exposures are not a major determinant for the initial onset of such symptoms.

Epidemiological studies of indoor nitrogen dioxide exposure and childhood asthma

In total, 13 studies of indoor nitrogen dioxide exposure and childhood asthma or respiratory symptoms were identified which were not included in previous reviews and employed quantitative exposure measures. These studies are summarized in Table 2 along with previously reviewed studies which employed quantitative exposure measures [5, 29-37].

A case-control study was conducted to explore the effect of indoor nitrogen dioxide exposure on respiratory symptoms in schoolchildren [38]. Cases suffered from bronchitis, asthma, frequent cough, or allergy as reported by a school physician. Controls were children from the same school without these symptoms. In each home, weekly average nitrogen dioxide levels were determined in kitchens, living rooms, and children's bedrooms using passive sampling devices. A questionnaire was used to gather information on potential confounders and

the final model adjusted for bedroom heating, maternal smoking, home humidity, parental education, parental respiratory symptoms, and child age and sex. VOC measures were not included and no significant relationship was detected between indoor nitrogen dioxide concentrations and childhood asthma. This study did report, however, that indoor nitrogen dioxide levels could not be well predicted simply by the presence of gas appliances.

Dijkstra et al examined the respiratory health effects of indoor nitrogen dioxide in a cross-sectional survey of Dutch children [39]. Weekly average nitrogen dioxide concentrations were determined in kitchens, living rooms, and child bedrooms, and a self-administered questionnaire was used to collect data on respiratory symptoms and confounding factors such as environmental tobacco smoke (ETS), dampness, parental education, and parental respiratory symptoms. Pulmonary function was assessed, but no measures of indoor VOCs were obtained. Home dampness was associated with cough and indoor ETS was associated with the development of wheeze, but no significant relationship was observed between indoor nitrogen dioxide exposure, lung function, or respiratory symptoms. Adjusting for potential confounders did not change this result. The authors note that it is possible that short term peaks in nitrogen dioxide exposure may be more important than weekly average exposures, but in general this study does not support a relationship between indoor nitrogen dioxide and childhood respiratory symptoms.

The respiratory effects of indoor nitrogen dioxide exposures were investigated in a cohort of asthmatic children identified from a cross-sectional health survey in South Australia [40]. Participants were selected if they reported asthma and had been symptomatic or had taken asthma medication within the last 12-months. Average indoor nitrogen dioxide exposures were determined over a 6-week period and on each monitoring day subjects were asked to record in a

diary whether or not they had experienced a variety of respiratory symptoms. The final model adjusted for age, sex, smoking, area of residence, asthma medication use, and education level as well as ambient sulfur dioxide, nitrogen dioxide, ozone, wind, relative humidity, minimum temperature, total fungal spore counts, cladosporium, and alternaria. A significant relationship was observed between indoor nitrogen dioxide exposure and chest tightness, daytime asthma attacks, and night asthma attacks on the same day as exposure. A significant 1-day lag effect was also observed for chest tightness and night asthma attacks. While no effect was observed for participants older then 14-years of age, this study does support a relationship between indoor nitrogen dioxide and asthma symptoms in younger children. However, no indoor measures were collected for VOCs or biological risk factors such as dust mite allergen, and therefore confounding by these types of exposures cannot be ruled out.

A Japanese cohort study was conducted to explore the effect of indoor and outdoor nitrogen dioxide on respiratory symptoms in children [41]. Participants were fourth grade students who attended one of nine elementary schools in seven different communities, and respiratory symptom data was collected from each student using a questionnaire completed by parents. Indoor nitrogen dioxide was measured in living rooms for 24-hours during both the summer and winter months, but no indoor VOC measures were collected. After adjusting for outdoor nitrogen dioxide, parental smoking, unvented heater use during winter, sex, child allergy, parental allergy, respiratory diseases under 2-years of age, and breast feeding, indoor nitrogen dioxide was associated with asthma prevalence among girls but not boys. As previously suggested [10], this difference may be due to girls spending more time in kitchens in closer proximity to sources of nitrogen dioxide such as gas stoves. However, outdoor nitrogen dioxide was associated with increased asthma incidence for all children even after adjusting for indoor

nitrogen dioxide levels. Therefore, this study suggests that nitrogen dioxide may promote asthma symptoms, but that both indoor and outdoor sources should be taken into account when assessing potential health effects.

Ponsonby et al conducted a cross-sectional survey to examine the relationship between nitrogen dioxide exposure and child lung function, as well as the potential modifying effect of house dust mite sensitization [42]. Children were selected from four randomly identified schools, and personal nitrogen dioxide exposure measures were collected for 2-days. Classroom nitrogen dioxide levels were also measured, and a questionnaire was used to gather information on home characteristics such as heating, gas cooking, parental smoking, and ventilation. Indoor VOC exposures were not investigated. Atopy was assessed by skin prick testing for a number of common allergens including house dust mites, and lung function was determined two to three days after the collection of nitrogen dioxide exposure measures. A questionnaire was used to collected data on asthma, recent wheeze, and other allergic diseases. After adjusting for child sex, number of siblings, breast feeding, and exposure to tobacco smoke, personal and total (including classroom measures) nitrogen dioxide exposure were not significant predictors of child asthma or recent wheeze. Increased personal exposure to nitrogen dioxide was associated with a significant reduction in the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) after cold air challenge, but this effect was not observed for mite sensitized children. Therefore, this study does not support a relationship between nitrogen dioxide exposure and childhood asthma, but suggests that nitrogen dioxide exposure may contribute to bronchial hyper-responsiveness among non-mite sensitized children.

The relationship between domestic nitrogen dioxide exposure and asthma prevalence was investigated in Australian pre-school children [43]. Participants were recruited from pre-school

health screenings, and parents were asked to complete a questionnaire regarding child respiratory symptoms, asthma, and other home characteristics such as cooking and heating fuels. Indoor nitrogen dioxide measurements were collected in children's bedrooms for 2 to 12-hours, but no indoor VOC measures were obtained. In this study, winter nitrogen dioxide levels were significantly greater than those in summer but no association was detected between indoor nitrogen dioxide levels and asthma prevalence.

A nested case-control study was conducted to investigate the relationship between recurrent wheezing and nitrogen dioxide exposure [44]. Parents answered questionnaires on housing characteristics, indoor environmental exposures, parental allergies, and child respiratory symptoms. Cases and controls had not moved since birth, and indoor nitrogen dioxide levels were monitored in the living room of each home for 4-weeks. Outdoor levels were also monitored over the same sampling period, and indoor air exchange rates were determined. Indoor VOC exposures were not investigated. After adjusting for parental allergy/asthma, gender, maternal age and smoking, breast feeding, and building age, indoor and outdoor nitrogen dioxide exposures were not significantly related to recurrent wheeze. However, risk estimates increased with increased exposure, and co-exposure to nitrogen dioxide and ETS was associated with a significantly increased risk of recurrent wheeze among children in the highest nitrogen dioxide exposure category relative to children in the lowest exposures who were not exposed to ETS. Therefore, this study suggests that a combination of exposures may be more relevant to the development of recurrent wheeze in children than exposure to nitrogen dioxide alone.

A randomized controlled trial of unflued gas heater replacement was conducted in 18 schools, with 10 control schools retaining their unflued gas heaters and eight replacing these with either electric heaters or flued gas heaters [45]. Eligible children had a history of physician

diagnosed asthma and did not have unflued appliances in their homes. Childhood asthma symptoms were collected from parents using telephone interviews every 2-weeks. Lung function and histamine challenge tests were performed at baseline and at the end of the study, and skin prick tests were performed at the end of the study. Nitrogen dioxide levels were measured in classrooms for 6-hours on 9-days spread out over the study period and homes were monitored for 3-days from the time of the child's arrival until bedtime. Significant reductions were observed in the intervention group for difficulty breathing during the day and night, chest tightness during the day, and asthma attacks during the day. Indoor nitrogen dioxide levels were also observed to be significantly lower in intervention schools, but there were no significant changes in lung function or response to histamine challenge between the intervention and control groups.

An American cohort study explored the association between indoor nitrogen dioxide exposure, maternal history of asthma, and childhood wheeze and persistent cough in the first year of life [46]. Women delivering babies in one of four Connecticut hospitals who already had a child with physician diagnosed asthma under 11-years of age were eligible. An in-home questionnaire was administered to each mother to gather information on child respiratory symptoms and parental history of asthma, and child respiratory symptoms were recorded on calendars provided to mothers. Indoor nitrogen dioxide was measured in the main living area for 10 to 14-days, and indoor allergen and fungal spore levels were also determined. After adjusting for dust mite, cockroach, cat, and dog allergen, as well as maternal education, ethnicity, gender, and smoking in the home, nitrogen dioxide exposures greater than 10 parts per billion (ppb) were associated with wheeze among children of mothers with and without physician diagnosed asthma. Furthermore, among infants of mothers with out asthma, indoor nitrogen dioxide was associated with persistent cough. In a separate analysis within the same population, this time

adjusting for season of sampling, parental asthma, ethnicity, maternal education, smoking in the home, daycare, living in an apartment, the presence of siblings, gender, and nitrous oxide exposure [47], infants living in homes with the greatest nitrogen dioxide exposures had a higher frequency of days with wheeze, persistent cough, and shortness of breath as compared to infants in homes with the lowest exposures. A third analysis, adjusted for age, ethnicity, medication use, season of sampling, mold/mildew, and water leaks was conducted for the older asthmatic siblings of these infants, and among children living in multi-family housing, each 20 ppb increase in nitrogen dioxide was associated with wheeze and chest tightness [48]. Together, these three studies [46-48] support a role for nitrogen dioxide exposures in promoting asthma symptoms among infants and older children. However, none of these studies included indoor VOC exposure measures and thus potential confounding by this type of exposure cannot be ruled out.

A cohort study was conducted to investigate the relationship between asthma symptoms, nitrogen dioxide, and dust-mite exposure among asthmatic children [49]. Children with doctor diagnosed asthma were identified using a questionnaire sent home with children at 18 elementary schools, and this questionnaire also addressed potential confounding factors such as age, gender, ethnicity, parental education, household smoking, hay fever, and respiratory illness before 2-years of age. Nitrogen dioxide was measured in kitchens for 3-days and in classrooms on three occasions for 3-days each. Dust-mite allergen levels (Der p 1) were determined in children's beds, lung function measures were recorded, and daily symptom diaries were kept for a period of 12-weeks. Significant increases in difficulty breathing during the day and night, chest tightness at night, and difficulty breathing after exercise were observed with each 10 ppb increase in classroom nitrogen dioxide, but home exposures were only associated with difficulty breathing at

night. However, kitchen nitrogen dioxide exposures were associated with a significant reduction in FEV_1, and when home and school exposures were combined a significant dose-response relationship was observed for difficulty breathing during the day and night and chest tightness at night. Among mite-sensitized children, exposure to mite allergen levels greater than 10 μg/g dust was associated with a significant increased rate of wheeze at night, daytime cough, and daytime asthma attacks after adjusting for nitrogen dioxide exposure. A significant interaction was also detected between mite-allergen exposure and nitrogen dioxide for wheeze at night. Although asthma symptoms were associated with nitrogen dioxide exposure in this study, the observed increases were relatively small and did not control for dust mite-allergen exposure. In general however, this study suggests that nitrogen dioxide may exacerbate asthma symptoms in children, but that this effect is less than that for dust mite allergen in mite-sensitized children.

Discussion

Childhood asthma and indoor VOCs

Three of the 4 studies reviewed detected a significant association between quantitative measures of indoor VOCs (primarily formaldehyde or total VOCs) and childhood asthma or respiratory symptoms [21,23,24]. The remaining study reported an increased risk of atopy with bedroom formaldehyde exposures, but this relationship was not statistically significant [22]. In general, these findings are consistent with previous studies [25,26] because they also reported an association between indoor formaldehyde and childhood asthma. While confounding by some unmeasured factor cannot be ruled out, confounding by indoor nitrogen dioxide in the 6 studies published since 1990 seems unlikely as all made an effort to control for this type of exposure. However, two studies relied on gas appliance use as a proxy measure of indoor nitrogen dioxide exposure and no actual exposure measures were obtained [22, 24]. Confounding by biological risk factors such as dust-mite allergen was also addressed in the majority of these studies as most either collected data on this type of exposure or performed skin prick tests to determine allergic status [21-24]. However, one study [26] did not collect data on biological risk factors such as dust-mite allergen, and the observed association could simply reflect the replacement of carpets with plastic flooring materials when in fact dust mites were the true cause of symptoms [4]. Nevertheless, available evidence suggests that exposure to indoor VOCs, and formaldehyde in particular, may contribute to the risk and/or severity of asthma symptoms in children. However, the increased risks of respiratory illness attributed to indoor VOC exposure tend to be rather modest, and the combination of indoor contaminants to which one is exposed may be more important than any individual type of exposure.

Childhood asthma and indoor nitrogen dioxide

In general, evidence for a relationship between indoor nitrogen dioxide exposure and childhood asthma is inconsistent. Only 6 of the 12 epidemiological studies reviewed detected significant increases in the risk of asthma or respiratory symptoms with indoor nitrogen dioxide exposure [40, 41, 46-49], and one intervention study reported a significant decrease in asthma attacks and difficulty breathing with decreased classroom nitrogen dioxide levels following replacement of unflued gas heaters [45]. In comparison, only 1 of the 9 previously reviewed studies reported a significant relationship between asthma and indoor nitrogen dioxide exposure [31]. Collectively, nearly all nitrogen dioxide studies conducted to date are limited in that they do not adjust for potential indoor VOC exposures. This is in contrast to studies of indoor VOCs, and is important because both types of exposures are common in indoor environments and are suspected to trigger the same types of symptoms. Therefore, while a relationship between indoor nitrogen dioxide exposure and childhood respiratory symptoms is suggested by several of the above investigations, evidence is far from conclusive and future investigations should include indoor VOC measures to adjust for this type of exposure. Furthermore, additional indoor contaminants should also be investigated, and one potential candidate may be UFPs. Provided next is a brief review of evidence suggesting a link between UFP exposures and asthma. A more thorough treatment is available elsewhere [28].

A case for the inclusion of UFP exposure measures in studies of childhood asthma

Of the suspected indoor chemical risk factors for childhood asthma, the effects of nitrogen dioxide and VOCs are most often studied. However, recent interest has focused on UFPs as an additional indoor risk factor for childhood asthma because these particles have been shown to trigger airway inflammation and oxidative stress in the lungs of experimental animals [51,52] and are produced indoors in large numbers [6]. In addition, several studies indicate that these particles are as strongly [54] or more strongly [55] associated with adverse respiratory effects than are larger particles. While epidemiological evidence is limited, some studies suggest that people with asthma or chronic obstructive pulmonary disease may be particularly susceptible to the respiratory effects of UFPs as deposition is greater in these individuals [56, 57]. Furthermore, UFP exposures have been shown to contribute to oxidative DNA damage in healthy adults, with indoor exposures contributing most to cumulative exposure levels due to the large amount of time people spend indoors [58]. In addition, because natural gas kitchen stoves have been identified as a significant risk factor for childhood respiratory symptoms even after adjusting for nitrogen dioxide levels [37], UFPs seem like logical targets for future investigations because they too are produced by such appliances. Indeed, other known sources of indoor UFPs such as electric baseboard heaters [50] have also been identified as significant risk factors for childhood asthma [31, 53].Therefore, there is currently a need for new research regarding the potential respiratory effects of indoor UFP exposures. However, in addressing this issue it will be important to include indoor measures of nitrogen dioxide and VOCs to assess potential interactions between these three common indoor air contaminants.

Conclusions

To date, a number of epidemiological investigations have explored the relationship between indoor nitrogen dioxide, VOCs, and childhood asthma. While a larger number of studies have focused on the effects of indoor nitrogen dioxide, indoor VOC exposure studies have been more consistent in demonstrating an association with asthma or related symptoms. Furthermore, the majority of indoor VOC exposure studies have controlled for potential confounding by nitrogen dioxide whereas indoor nitrogen dioxide exposure studies have generally not controlled for indoor VOC exposures. Nevertheless, evidence to date suggests that any increase in asthma risk that may be associated with indoor VOC or nitrogen dioxide exposure is likely to be small. As a result, future studies should explore the effects of other common indoor air contaminants such as UFPs because these particles are known triggers of airway inflammation and might also contribute to the frequency and/or severity of asthma symptoms in susceptible individuals.

TABLES

Table 1 Reported findings of epidemiological studies of childhood asthma and indoor VOCs

Reference	Study Design, Population, and Location	Outcome	VOC	Results OR (95% CI) or p-value	NO_2 exposure included in analysis
Krzyanowski et al., 1990 [26]	*Cross-sectional* 298 children 6-15 years of age, USA	Doctor diagnosed asthma	Formaldehyde (kitchen) (> 74 μg/m^3)	p<0.03	Yes
Smedje et al., 1997 [21]	*Cross-sectional* 627 school children 13-14 years of age, Sweden	Current asthma	Formaldehyde (> 5 μg/m^3) Total VOCs (per 10 μg/m^3)	1.1 (1.01, 1.2) 1.3 (1.1, 1.5)	Yes
Garrett et al., 1999 [22]	*Cross-sectional* 148 children 7-14 years of age, Australia	Atopy	Formaldehyde (Bedroom) (per 10 μg/m^3)	1.4 (0.98, 2.0)	Yes
Rumchev et al., 2002 [25]	*Case-control* 88 asthma cases and 104 controls aged 6-months to 3-years, Australia	Doctor diagnosed asthma	Formaldehyde (>60 μg/m^3)	1.39 (1.1, 1.7)	Asked about gas appliance use
Venn et al., 2003 [24]	*Case-control* 193 cases with persistent wheezing illness and 223 controls aged 9-11 years, Britain	Wheezing illness	Total VOCs (> 506 μg/m^3) Formaldehyde (> 32μg/m^3)	0.85 (0.48, 1.52) 1.04 (0.59, 1.82)	Yes
		Persistent wheezing illness among cases			
		Night-time symptoms	Total VOCs (> 506 μg/m^3) Formaldehyde (> 32μg/m^3)	1.65 (0.61, 4.43) 3.33 (1.23, 9.01)	
		Daytime symptoms	Total VOCs (> 506 μg/m^3) Formaldehyde (> 32μg/m^3)	0.85 (0.48, 1.52) 1.04 (0.59, 1.82)	
Rumchev et al., 2004 [23]	*Case-control* 88 asthma cases and 104 controls aged 6-months to 3-years, Australia	Doctor diagnosed asthma	Per 10 μg/m^3 increase in: Total VOCs Benzene Toluene Ethylbenzene m-Xylene Dichlorobenzene	 1.27 (1.17, 1.37) 2.92 (2.25, 3.79) 1.84 (1.40, 2.41) 2.54 (1.16, 5.56) 1.60 (1.10, 2.34) 1.55 (1.27, 1.88)	Asked about gas appliance use

Table 2 Reported findings of epidemiological studies of childhood asthma and indoor nitrogen dioxide

Reference	Study Design, Population, and Location	Outcome	NO_2 Measurement Location	Results OR(95% CI) or p-value	VOC Exposure Measure Included
Florey et al., 1979[29]	*Cross-sectional* 808 children aged 6-7 years, Britain	Respiratory illness	Bedroom	p~0.05	No
Melia et al., 1982[35]	*Cohort* 191 children aged 5-6 years, Britain	Respiratory symptoms	Bedroom Living room	p>0.3 p<0.1	No
Hoek et al., 1984[38]	*Case-control* 128 cases and 103 controls 6 years of age	Asthma		OR (90% CI) per unit increase in 10log NO_2(ppb)	No
			Kitchen Living room Bedroom	1.29 (0.40, 5.4) 5.83 (0.70, 34.9) 2.68 (0.40, 16.2)	
Koo et al., 1990[36]	*Cross-sectional* 362 primary school children, China	Asthma	Personal sampler	p=0.42	No
Dijkstra et al., 1990[39]	*Cross-sectional* 775 children aged 6-12 years, Holland	Asthma	Combined average from kitchen, living room, and bedroom:		No
			21-40 $\mu g/m^3$ 41-60 $\mu g/m^3$ > 60 $\mu g/m^3$	0.67 (0.32, 1.41) 0.34 (0.08, 1.54) 0.56 (0.15, 2.06)	
Neas et al., 1991[30]	*Cohort* 1567 children aged 7-11 years, United States		Household mean	OR per 15 ppb increase in NO_2	No
		Asthma		0.91 (0.60, 1.36)	

Table 2 continued

Reference	Study Design, Population, and Location	Outcome	NO_2 Measurement Location	Results OR (95% CI) or p-value	VOC Exposure Measure Included
Infante-Rivard, 1993[31]	*Case-control* 457 asthma cases and controls aged 3-4 years, Canada	Asthma	Personal samplers: < 0.5-10 ppb 10-15 ppb >15 ppb	 0.95 (0.31, 2.95) 3.85 (0.92, 16.09) 19.8 (4.75, 83.03)	Asked about urea formaldehyde insulation
Samet et al., 1993[33]	*Cohort* 1205 infants followed until 18-months of age, United States	Respiratory illnesses	Bedroom: 20-40 ppb > 40 ppb	 1.04 (0.96, 1.12) 0.94 (0.81, 1.08)	No
Pilotto et al., 1997[32]	*Cohort* 388 children aged 6-11 years, Australia	 Wheeze Cough with phlegm	Classrooms and personal measures at home: >40 ppb >40 ppb	 1.41 (0.63, 3.15) 1.28 (0.76, 2.15)	No
Farrow et al., 1997[34]	*Cross-sectional* 1200 infants aged 3-12 months, Britain	 Cough Breathlessness Wheezing	Bedroom	OR for doubling NO_2 1.01 (0.86, 1.18) 0.91 (0.58, 1.43) 1.13 (0.90, 1.43)	No
Garrett et al., 1998[37]	*Cross-sectional* 148 children aged 7-14 years in 80 homes, Australia	Asthma	 Bedroom Indoor mean	OR per 10 $\mu g/m^3$ increase in NO_2 1.01 (0.75, 1.37) 1.00 (0.75, 1.31)	No
Smith et al., 2000[40]	*Cohort* 48 asthmatic children aged ≤14 years	 Daytime asthma attacks Night asthma attacks Chest tightness	Average personal exposure	 1.13 (1.02, 1.26) 1.16 (1.03, 1.30) 1.29 (1.16, 1.43)	No

Table 2 continued

Reference	Study Design, Population, and Location	Outcome	NO_2 Measurement Location	Results OR (95% CI) or p-value	VOC Exposure Measure Included
Shima et al., 2000[41]	*Cohort* 842 primary school children, Japan	Asthma	Indoor mean:	OR per 10 ppb increase in NO_2	No
			4^{th} Grade		
			boys	0.77 (0.48, 1.20)	
			girls	1.63 (1.06, 2.54)	
			5^{th} Grade		
			boys	0.92 (0.60, 1.39)	
			girls	1.67 (1.06, 2.66)	
			6^{th} Grade		
			boys	0.78 (0.45, 1.30)	
			girls	1.18 (0.62, 2.18)	
Ponsonby et al., 2001[42]	*Cross-sectional* 344 primary school children, Australia		Personal exposure	Relative risk per 1 ppb increase in NO_2	No
		Asthma		0.99 (0.97, 1.02)	
		Wheeze		1.00 (0.97, 1.02)	
		FEV_1/FVC after cold air challenge		-0.12 (-0.23, -0.01)	
Ciuk et al., 2001[43]	*Cross-sectional* 1121 children 4-years of age, Australia	Asthma	Bedroom	No association between asthma and indoor NO_2 (p-value or OR reported not reported)	No
Emenius et al., 2003[44]	*Case-control* 181 cases and 359 controls 1-2 years of age	Recurrent wheezing	Living room:		No
			8.4-11.6 $\mu g/m^3$	0.96 (0.52, 1.77)	
			11.7-15.6 $\mu g/m^3$	1.08 (0.57, 2.03)	
			>15.6 $\mu g/m^3$	1.51 (0.81, 2.82)	

Table 2 continued

Reference	Study Design, Population, and Location	Outcome	NO_2 Measurement Location	Results OR (95% CI) or p-value	VOC Exposure Measure Included
Pilotto et al., 2004[45]	*Intervention* 118 children primary school children, 45 children in the intervention group and 73 in the control group, Australia		Classrooms. NO_2 levels were significantly lower in intervention schools ($p<0.001$).	Relative risks for intervention vs control children:	No
		Asthma attacks during the day		0.39 (0.17, 0.93)	
		Asthma attacks at night		0.38 (0.13, 1.07)	
		Missed school due to asthma		1.34 (0.68, 2.60)	
		Asthma medication use		0.77 (0.49, 1.21)	
		Difficulty breathing during the day		0.41 (0.07, 0.98)	
		Difficulty breathing at night		0.32 (0.14, 0.69)	
		Visit Hospital for asthma treatment		0.60 (0.35, 1.03)	
Belanger et al., 2003[46]	*Cohort* 849 infants followed for the first year of life, United States		Living room:	OR per 10 ppb increase in NO_2	No
		Wheeze	Mothers with asthma	1.10 (0.87, 1.40)	
			Mothers without asthma	1.10 (0.96, 1.25)	
		Persistent cough	Mothers with asthma	1.01 (0.81, 1.26)	
			Mothers without asthma	1.21 (1.05, 1.40)	
Van Strien et al., 2004[47]	*Cohort* 768 infants followed for the first year of life, United States		Living room:	Rate Ratios	No
		Wheeze	5.1-9.9 ppb	1.15(0.79, 1.67)	
			9.9-17.4 ppb	1.03 (0.69, 1.53)	
			>17.4 ppb	1.45 (0.92, 2.27)	
		Persistent cough	5.1-9.9 ppb	0.96 (0.69, 1.36)	
			9.9-17.4 ppb	1.33 (0.94, 1.36)	
			>17.4 ppb	1.52 (1.00, 2.31)	
		Shortness of breath	5.1-9.9 ppb	1.59 (0.96, 2.62)	
			9.9-17.4 ppb	1.95 (1.17, 3.27)	
			>17.4 ppb	2.38 (1.31, 4.34)	

Table 2 continued

Reference	Study Design, Population, and Location	Outcome	NO_2 Measurement Location	Results OR (95% CI) or p-value	VOC Exposure Measure Included
Belanger et al., 2006[48]	*Cohort* 728 children < 12 years of age, United States		Living rooms in multi-family housing complexes	OR per 20 ppb increase in NO_2	No
		Wheeze		1.52 (1.04, 2.21)	
		Persistent cough		1.06 (0.75, 1.49)	
		Shortness of breath		1.28 (0.85, 1.91)	
		Chest tightness		1.61 (1.04, 2.49)	
Nitschke et al., 2006[49]	*Cohort* 174 children aged 5-13 years		Classrooms	Relative rate per 10 ppb increase in NO_2	No
		Asthma attacks during the day		1.03 (0.99, 1.08)	
		Asthma attacks at night		1.00 (0.93, 1.08)	
		Difficulty breathing during the day		1.09 (1.03, 1.15)	
		Difficulty breathing at night		1.11 (1.05, 1.18)	
		Chest tightness during the day		1.08 (0.99, 1.19)	
		Chest tightness at night		1.12 (1.07, 1.17)	
		Difficulty breathing after exercise		1.04 (1.01, 1.09)	
		Asthma attacks during the day	Kitchens	1.00 (0.95, 1.05)	
		Asthma attacks at night		1.04 (1.00, 1.07)	
		Difficulty breathing during the day		1.00 (0.98, 1.03)	
		Difficulty breathing at night		1.03 (1.01, 1.05)	
		Chest tightness during the day		0.97 (0.89, 1.06)	
		Chest tightness at night		1.02 (0.95, 1.09)	
		Difficulty breathing after exercise		0.97 (0.92, 1.02)	

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APPENDIX 2. BROCHURE AND QUESTIONNAIRE FOR RESIDENTIAL UFP STUDY

SUMMARY

Beginning in November 2005, we are looking for participants living in detached homes with either wood stoves, electric baseboard heaters, gas furnaces, or oil furnaces as their primary type of heating system. As a participant, you will be asked to complete a short questionnaire, and one 8-hour indoor air quality measurement will be collected overnight in your home at your convenience. You will not be paid for your participation, but the information collected in your home will help improve future studies of common childhood diseases like childhood asthma.

Thank you very much.

Sincerely,

Scott Weichenthal

Are you Interested in Participating in a Study of Indoor Air Quality and Home Heating Systems?

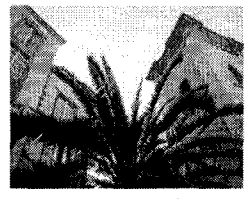
If you are interested in participating, please contact Scott Weichenthal by telephone or by email for more information.

Phone: 514-495-2905

email: sweich@po-box.mcgill.ca

AllerGen McGill

Participants Needed for a McGill University Public Health Study



Indoor Air Quality and Home Heating Systems

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Indoor Air Quality and Home Heating Systems

Introduction

In this study, we are interested in examining indoor air quality in homes with different types of heating systems. We are specifically interested in indoor ultrafine particles (UFPs) because these particles are sometimes produced by heating systems and may contribute to the risk of childhood asthma. However, people without children are also eligible to participate. If you agree, your participation will consist of answering a short questionnaire and allowing researchers to collect one 8-hour indoor air quality measurement in your home. This study is funded by the Allergy, Genes and Environment Network (AllerGen) which is a new federal network that has recently launched a national, integrated research program focused on allergic disease, genes and the environment. Ours is an environmental study, and roughly 100 families will participate in this new project over the next two years.

Questionnaire

As a participant, you will be asked to complete a short questionnaire. This questionnaire will address general home characteristics (e.g. age and size of home, type of building materials, etc.) as well as more specific questions regarding your home's current heating system or the use of portable heating devices.

Indoor Air Quality Measurements

Indoor measurements will be collected overnight during the winter heating months using two programmable, quiet, direct reading instruments. These instruments will measure indoor UFPs, CO_2, temperature, and humidity in two locations in the home for 8-hours (the main living area and one bedroom). The instruments are safe, and will be dropped off and picked up at your convenience.

Confidentiality

The information collected in your home will be used to develop a model for the prediction of indoor air contaminants, primarily UFPs, for use in future studies. In this process, some or all of the data collected in your home may be published. However, care will be exercised to maintain confidentiality, and the data you provide will be identified only by category of heating system in all communications or publications. You will be provided with the results from your home along with Canadian standard values when available.

If you are interested in participating, please contact Scott Weichenthal by telephone or by email for more information.

Phone: 514-495-2905

email: sweich@po-box.mcgill.ca

AllerGen McGill

I. General Home Characteristics **Code:**_____

Date:_____

Address:_____

1. Year of home construction: _____

2. Type of building materials (brick, aluminum siding, etc):_____

3. Does the home have an attached garage? Yes/No

4. What type of insulation is in the home?_____

5. Does the home have wall-to-wall carpeting? Yes/No

6 a) Does the home have an air purifier? Yes/No

b) Does the home have a humidifier/dehumidifier? Yes/No

c) Does the home have a ventilation system? Yes/No

7. Does the home have central air conditioning? Yes/No

8. Type of hot water heater (Electric, Gas, Oil, Other):_____

9a. Type of clothes dryer (Electric, Gas, Oil, Other):_____

9b. Was the clothes dryer used during the sampling period? Yes/No

9c. If the clothes dryer was used, at what time and for how long was it used?

_____

10. Estimated home size (square feet):_____

11. Number of Windows Open During Sampling:_____

12. How often do you dust?_____

13. How often do you vacuum?:_____

14. Number of People in home:_____

15. Does the kitchen open into the main living area? Yes/No

II. Home Cooking System

16. Type of kitchen stove (Electric, Natural Gas, Other):_____

a) Exhaust fan present? Yes/No

b) Exhaust fan used during last cooking period? Yes/No

c) Does the exhaust fan vent to the outside? Yes/No

17. On the day of sampling, how long did the dinner cooking period last (approximate number of minutes)?:_____

18. On the day of sampling, what time did the dinner cooking period end?:

_____

19. On the morning after sampling, at approximately what time will cooking begin?_____

20. On the day of sampling, what cooking appliances were used during the dinner cooking period?:

a). Stove-Top Elements: Yes/No

Number of Elements Used:_____

Approximate Duration:_____

b). Oven: Yes/No

Approximate Duration:_____

c). Other (Specify):_____

Approximate Duration:_____

III. Cigarette Smoking and Burning Candles

21. Do any members of your home smoke cigarettes? Yes/No

If Yes:

a) How many members smoke?_____

b) Do they smoke inside the home? Yes/No

22. Were any candles burned inside the home on the day of sampling? Yes/No

IV. Portable Heaters

23. Do you own a portable heater? Yes/No

If Yes:

a) What type of heater is it? Electric/Gas/Kerosene/Other_____

24. On the sample day, were any portable heaters used? Yes/No

If Yes:

a) Where was the portable heater located?_____

b) Approximately how long was it used?_____

V. Fireplaces

25. Does your home have a fireplace? Yes/No

If Yes:

a) What type (Natural Gas/Oil/Electric/Wood)?_____

b) Was the fireplace used on the sampling day? Yes/No

VI. Characteristics of Electric Baseboard Heaters

26. Approximately how old are the baseboard heaters?_____

27. Approximately how often are the baseboard heaters cleaned?_____

28. At approximately what date did you begin using your electric baseboard heaters this year?_____

29. How long has it been since the baseboard heaters were last cleaned?_____

30. What is the total number of electric baseboard heaters in the home?_____

31. How many of the baseboard heaters are normally used?_____

32. How many electric baseboard heaters are located in the main living area?_____

33. How many electric baseboard heaters are located in the kitchen?_____

VI. Characteristics of Central Air Oil/Gas Furnace

26. Approximately how old is your central air gas furnace?_____

27. Approximately how often is your furnace cleaned?_____

28. How long has it been since your furnace was last cleaned?_____

29. What type of filter is installed in your furnace?_____

30. How long has it been since your duct work was last cleaned?_____

31. What is the total number of hot air supply vents in the home?_____

32. How many hot air supply vents are located in the main living area?_____

33. How many hot air supply vents are located in the kitchen?_____

34. Does your furnace have a chimney vent or a direct vent?_____

VI. Characteristics of Wood Stove

26. Approximately how old is your wood stove?_____

27. Approximately how often is your stove/chimney cleaned?_____

28. How long has it been since your stove/chimney was last cleaned?_____

29. How long is your wood normally allowed to dry prior to burning?_____

30. Where in the home is the wood stove located?_____

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal

CONSENT FORM

Project Title: Estimation of Indoor Ultrafine Particle Levels in Single Family Homes

Researchers:
Primary Researcher: Dr. Claire Infante-Rivard, MD, PhD
Collaborator: Dr. Andre Dufresne, PhD

Nature of the Project:

In this study, we are primarily interested in examining the indoor air quality of single family homes with different types of heating systems. We are specifically interested in the presence of indoor ultrafine particles because these particles may contribute to the risk of childhood asthma. If you agree, your participation in this project will consist of two things: completing a questionnaire which deals with your home's indoor environment (e.g. number of smokers, type of heating system, type of cooking system, use of candles, etc), and permitting researchers to collect one 8-hour overnight measurement of indoor ultrafine particles, as well as measurements for indoor temperature, humidity, and carbon dioxide. All measurements will be collected using small, quiet instruments that will be positioned out of reach of children although we acknowledge that these instruments are not dangerous. We will use the measures collected in your home to develop a predictive model for indoor ultrafine particles in single family homes, and apply this model in future studies of childhood asthma.

This project is supported by the AllerGen network which is a participant in the federal government's Networks of Centers of Excellence program. Allergen an integrated research program focused on allergic disease, genes and the environment. The Allergen website is available at http://www.allergen-nce.ca/.

What is Involved in the Project?

All in-home measurements will be collected between the hours 11:00pm and 7:00am. The instruments used to collect this data will be small (P-Trak: 27 cm x 14 cm x 14 cm, 1.7 kg;
Q-Trak: 10.7 cm x 18.3 cm x 3.8 cm, 0.59 kg), quiet, and non-disruptive, and will be pre-programmed as not to require participant operation. Ultrafine particle measurements will be collected in the main living area and in an adult bedroom using two P-Trak instruments. Indoor temperature, humidity, and carbon dioxide will be measured in the main living area using one Q-Trak. In all homes instruments will be placed out of reach of children. A time will be arranged at the participants convenience for one researcher to visit the home and set up the instruments, and the questionnaire will be completed at this time. A researcher will return the following day to collect the instruments at the participants' convenience. The participants role will be to complete the questionnaire in full and to ensure that their home's heating system is active during the sampling period.

3175, Côte-Sainte-Catherine
Montréal (Québec)
H3T 1C5

What are the Risks of this Study?

There are few, if any risks associated with operating either of the instruments to be used in this study inside the home. While the P-Trak does contain a small amount of solvent (8 mL), this solvent is absorbed on a wick that is locked inside the instrument and will not be removed at any point inside the home. However, even if all of the solvent from the two P-Traks were to evaporate in one small enclosed room with dimensions 3m x 3m x 3m (closet size), the airborne concentration would be less than half that permitted in an occupational setting and more than one hundred times less than the lower flammable limit. Therefore, we do not consider the use of these instruments in the home to be in any way a risk to participant health or safety. However, the instruments will be calibrated prior to each sampling period and the integrity of the instrument casing will be checked to minimize the likelihood of any incident.

What are the Benefits of Participating?

We are aware that your participation in this study will not bring you immediate benefit. However, your participation will help us to further understand the role of indoor air pollution in childhood asthma. As such, we strongly hope you will agree to participate in our study because your collaboration is essential to help us better understand this disease. Furthermore, we will be delighted to submit to you the results of our assessment along with Canadian standards if available. However, should a member of your family have asthma, we will not be able to establish a correlation between indoor ultrafine particle levels and their asthma symptoms.

How will your Confidentiality be Assured?

All information obtained from your residence in the context of this research project will be confidential unless authorization is obtained on your part or permitted by law. All measures will be taken to assure the confidentiality of your data; the information collected in your home will be anonymized and linked to your residence only by a number (e.g. residence number 25). In order to ensure that our research is conducted responsibly, it is possible that a delegate of the Research Ethics Committee or sponsoring agency will look at our research data. In addition, the results of this research could be published or presented in a communication or in a scientific conference; but any information that could identify your residence or your family will not be revealed.

Responsibility of Researchers

Signing this form in no way waives your legal rights nor releases the investigators or sponsors of this research from their legal or professional responsibilities should a situation arise to cause you prejudice.

Your Rights as a Participant

Your participation in this study is voluntary. The decision you make will not affect the quality of health services offered to your family should they ever require them at the Ste. Justine Hospital. Furthermore, you will be able to withdraw from the study at any time and request that information about your home be destroyed.