HUMAN PULMONARY FUNCTION RESPONSE TO A CONTROLLED EXPOSURE TO FINE URBAN PARTICULATE MATTER

by

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A thesis submitted in conformity with the requirements
for the degree of Master of Science
Graduate Department of Community Health
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Abstract

There is growing evidence that fine particulate matter may have adverse effects on respiratory health, but convincing human exposure studies are lacking. The present thesis describes preliminary research in which four human subjects were exposed for two hours on four separate occasions each to particle-filtered air and to three target levels of concentrated ambient fine particles (20, 40, and 60 $\mu g/m^3$) in a human exposure facility using a new and innovative particle delivery method. Diffusing capacity for CO, body plethysmography, and spirometry were carried out before and after exposure. Spirometry was also carried out during each exposure. Results suggested that the facility could effectively be used for human exposures to concentrated fine ambient particles while maintaining adequate conditions of safety and comfort, and that two-hour exposures up to target concentrations of 60 $\mu g/m^3$ did not adversely alter lung function in the subjects tested.

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My individual contribution to the work described in this thesis was limited to: *analysis of the literature; measurement of exposure facility settings and environmental conditions as described; administration of pulmonary function tests as described; statistical analyses; interpretation of the data.*

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations and Symbols

AD	Aerodynamic diameter
ASHRAE	American Society of Heating, Refrigeration, and Air Conditioning Engineers
ATS	American Thoracic Society
D_{LCO}	Diffusing capacity for carbon monoxide
CEOHA	Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society
CoV	Coefficient of variation
EC	Exposure chamber
EPA	United States Environmental Protection Agency
f	Number of breaths taken in one minute
FA	Filtered air
FEF_{25}	Forced expiratory flow rate when 25% of the FVC has been exhaled
FEF_{25-75}	Forced mid-expiratory flow rate
FEF_{50}	Forced expiratory flow rate when 50% of the FVC has been exhaled
FEF_{75}	Forced expiratory flow rate when 75% of the FVC has been exhaled
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
H_2SO_4	Sulphuric acid
HAPC	Harvard ambient particle concentrator
HEF	Human exposure facility
HEPA	High efficiency particulate air
IC	Inspiratory capacity
NIOSH	National Institute for Occupational Safety and Health
PEF(R)	Peak expiratory flow rate
PFV	Pulmonary function variable
PM	Particulate matter suspended in the air
$PM_{2.5}$	Particulate matter of aerodynamic diameter 2.5 microns or less
PM_{10}	Particulate matter of aerodynamic diameter 10 microns or less
PME	Particulate matter exposure

Raw	Airway resistance
RV	Residual volume
sb	Single breath
SO_4^{2-}	Sulphate
SRaw	Specific airway resistance (R_{AW}/TGV)
TD	Thermodynamic diameter
TGV	Thoracic gas volume
TLC	Total lung capacity
TSP	Total suspended particulate matter
VC	Vital capacity
Ve	Volume of air breathed in one minute
VMM	Ventilation measurement module
VOC	Volatile organic compound

Chapter One: Introduction

Concern for the possible health effects of fine particulate matter exposure on human health has become an important issue in Canada. Several government bodies at the provincial (Ontario) and federal (Canadian) level have commissioned extensive examinations of the health risks of such exposure, the benefits of reducing exposure, and the strategies by which such reductions may feasibly be implemented. These government organizations include the Canadian Environmental Protection Agency, the Federal-Provincial Action Committee Working Group on Air Quality Objectives and Guidelines, the Joint Industry/Government "Sulphur in Diesel and Gasoline Fuels" Steering Committee, the Ontario Ministry of the Environment Smog Plan Steering Committee, and the Canadian Council of Ministers of the Environment. [1,2,3,4,5]

Many epidemiological studies on the health effects of air pollution have found small but statistically significant associations between exposure to particulate matter and mortality and/or morbidity. Exposure measures which have been linked to health outcomes have included mass concentration of total suspended particulate (TSP), mass and number concentration of particulate matter of aerodynamic diameter less than or equal to 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$), and mass concentrations of various components of particulate matter, such as sulphuric acid (H_2SO_4), sulphate (SO_4^{2-}), and particle strong acidity (H^+). Health outcome measures have included total mortality, respiratory mortality, cardiac mortality, cardiopulmonary mortality, hospital admissions or emergency room visits for respiratory and cardiac complaints, days off school or work, changes in medication use, and acute changes in pulmonary function.[6]

While the available epidemiological evidence has led to the hypothesis that particulate matter may be a contributing factor to cardiopulmonary disease, it does not demonstrate causality. Support from controlled experiments is required to elucidate the nature of the relationships observed. For the health effects of particulate matter, this evidence is limited. Some animal studies have demonstrated that particulate matter exposure (PME) can cause changes in lung function, airway reactivity, and mucociliary clearance.[7,8] There is also evidence from some cell studies that PME can trigger pro-inflammatory and inflammatory reactions, and impair host defences.[8] In humans, controlled trials have also demonstrated some positive findings with sulphuric acid exposure, but most studies have found little or no change.[6,8]

One weakness of experimental research into the health effects of PME is that most often only one fraction of the complex combination of constituents that comprise particulate matter has been used in the exposure. For example, many studies have used only sulphate or sulphuric acid particles alone or in simple combinations with pollutant gases. It may be that the many components that make up the ambient particle mixture interact to create its toxic effect,[9,10,11] or that the key component has not yet been tested. If either case were true, then the effects seen in epidemiological studies would not be confirmed by such experimental research. Furthermore, studies which attempted to model ambient exposures have shortcomings. For example, collected ambient particles have been re-suspended and then delivered, but re-suspension has been found to alter the composition (e.g. loss of volatile components, adsorption of gas-phase components).[11] New concentration techniques using virtual impactors have enabled researchers to concentrate ambient particles while maintaining them in the airborne state, thus bypassing this problem.[9,11] These techniques have been incorporated into the design of the Harvard ambient particle concentrator.

The research reported here was undertaken to assess the feasibility of a human exposure facility that used the Harvard ambient particle concentrator as a particle delivery method for testing the human health effects of fine particulate matter exposure. The objectives of this thesis were: first, to document the characterization of the human exposure facility; and second, to relate the preliminary findings on the human pulmonary function response to controlled exposures to concentrated ambient particles, using that facility.

In order to satisfy these objectives, the following hypotheses were tested:

1. That independent measures of $PM_{2.5}$ concentration (DustTrak aerosol monitor and gravimetric analysis of filter samples) are in good agreement, and can therefore provide complementary data on exposure.
2. That stable target concentrations of $PM_{2.5}$ can be achieved in the exposure chamber (EC) using ambient air as the particle source, by adjustment of the human exposure facility settings.
3. That EC temperature and relative humidity remain within a comfortable range, and that EC pollutant gas concentrations do not differ from ambient levels, throughout each exposure trial.

4. That exposure to controlled concentrations of $PM_{2.5}$ has a concentration- and time-dependent effect on pulmonary function.

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Chapter Two: Review of the respiratory health effects of particulate matter

Introduction

Particulate matter suspended in the air (PM) consists of solid and liquid material representing a wide variety of chemical constituents that remains suspended in the air for an extended period of time due to its small size. The small size of this particulate matter also allows it to penetrate deep into the respiratory tract, where it may exert an adverse health effect. Epidemiological data suggests that acute and chronic particulate matter exposure (PME) at ambient levels may be associated with various measures of mortality and morbidity. Animal and cell studies are beginning to reveal mechanisms whereby such effects may occur. Rigorous clinical studies of the health effects of ambient particle exposures are required to complement and complete the available epidemiological and toxicological data.

Deposition

PM includes dust, smoke, pollen and other substances emitted by natural sources and human activities.[1,2] Of primary concern is particulate matter that is small enough to reach the gas-exchange portion of the lung.[3] Several models of particulate matter deposition in the lung have been developed in order to estimate exposure risk. One that is widely used was developed by the International Commission on Radiological Protection.[4,5,6] The ICRP model of deposition compartmentalizes the lung into three regions, the extrathoracic region, (ET_1, the anterior nares, and ET_2, the posterior nasal passages, larynx, pharynx, and mouth), the bronchial region (from the trachea to the bronchi, i.e. airway generations 0 to 8, designated BB), the bronchiolar region (airway generations 9 to 15, designated bb) and the alveolar interstitial region (comprising the respiratory bronchioles, alveolar ducts, atria, alveoli, and alveolar sacs, i.e. airway generations 16 to 26, designated AI).[6]

According to the model, the proportion of aerosols present in the breathing zone that deposit in each region of the respiratory tract is largely determined by particle parameters such as size, shape, and density. In the ICRP model, particulate matter is treated as a log-normal distribution of particles of different aerodynamic or thermodynamic diameters. Aerodynamic diameter (AD) is defined as the diameter of a hypothetical sphere of unit density having the same terminal velocity as the particle in question. The terminal velocity is the velocity reached

when a particle's gravitational acceleration is balanced by its fluid resistance. AD is useful for particles whose deposition is determined by impaction and sedimentation. Thermodynamic diameter (TD) is the diameter of a spherical particle having the same diffusion coefficient in air as the particle of interest. TD is useful for particles whose deposition is principally governed by diffusion. [5,6]

The model, which is based on both experimental and theoretical work, predicts that when the median aerodynamic (or thermodynamic in the case of very small particles) diameters of a log-normal particle distribution are plotted against the estimated mass deposition in each compartment of the lung, little variability is seen. The model also indicates that larger particles are preferentially deposited in the nasopharynx (ET_1 and ET_2), but smaller particles are much more likely to penetrate deeper into the lung before depositing. Aerosols of median AD 10 μm or less have a much greater chance of depositing beyond the extrathoracic region. Deposition also depends on hygroscopic growth of the particle within the lung, the shape and dimension of the airway and alveolus, the ventilatory pattern, type of breathing (oral vs. nasal), respiratory secretions, and the efficiency of clearance mechanisms, and the ICRP model can be adapted to meet many of these conditions.[3,5,6,7]

Since physical characteristics largely determine where the particle will deposit, they also determine the toxicity of the particle to some extent, since the distal regions of the lung are less effective in clearing foreign material, and are naturally more sensitive to damage.[3,4,7]

Composition

Particle toxicity is also determined by its chemical composition, which dictates how it will react with the tissue.[3,4,7] For example, metals such as mercury and cadmium, and combustion-derived organic compounds, are highly toxic because of their chemical properties and how they interact with biological tissue.[7]

The composition of ambient particulate matter (PM) is varied, and can be roughly categorized according to size.[2,7] Coarse particulate, in the size range 2.5 - 10 μm, consists of dust (e.g. soil dust, coal and fly ash, etc.), oxides of silicon, aluminum, magnesium, titanium, and iron, calcium carbonate, sodium chloride, and pollen, mould spores, and other organic

material.[2,6] Fine particulate, in the size range of 0.1 to 2.5 μm, consists of hydrogen ion, sulphate, nitrate, and ammonium ions, organic compounds, hydrocarbons (including polycyclic aromatic hydrocarbons), carbon, metals such as lead, cadmium, vanadium, nickel, copper, and zinc, particle-bound water, and biogenic organics.[2,6] Ultrafine particulate, in the size range of 0.01 to 0.1 μm, consists of atmospheric dusts, metal oxide fumes, some products of combustion, viruses, and various other components present in smaller quantities.[2,8]

Acid aerosols are an important component of fine particulate matter from a health effects perspective. SO_2 can undergo an oxidation reaction with H_2O, O_2, and other materials to form other sulphur-containing species, which when adhered to solid particles or dissolved in liquid become part of the particulate matter mix. The sulphur-containing aerosol may exist as an acid droplet or can be converted to sulphates in the presence of ammonia, which is found in ambient air and also in the airways. Most sulphate or sulphuric acid particles have an aerodynamic diameter less than one micron, but acidic fog droplets may be in the range of 2 to 10 μm. [3,9]

The elemental chemical composition of fine particulate matter in Toronto was analyzed by Paciga[10] and by Pringle[11], and their data is reproduced in Table 2-1. It was found that elements such as Al, Ca, Fe, La, Mg, Sc, Na, and Ti were usually concentrated on larger particles and were not especially enriched (compared to natural levels). Elements such as Pb, Br, Cl, V, Zn, I, As, and Sb were usually concentrated on smaller particles and their concentrations were elevated compared to natural levels. Other elements were less easy to categorize.[10,11]

Measurement

Many different measures of PME are in general use. Two older measures are coefficient of haze (CoH) and British or Black smoke (BS), both of which measure the change in optical properties of the filter on which the sample is collected, and thus place more emphasis on the carbon constituents of the sample, most of which are in the fine size range, since they are most effective in absorbing light.

Table 2-1. Mean concentration and approximate size of elements in PM in Toronto

Element	Concentration (ng/m^3) (Mean of 52 24-hour samples) [11]	Mean concentration (ng/m^3) (Mean of 107 24-hour samples) [10]	Approximate Mass Median Diameter (μm)[10]
Al	920	2100	8
As	3.9	12	1.5
Br	58	290	0.3
Ca	3240	5300	7
Ce	>1.4	-	-
Cl	2580	1200	0.6
Co	0.57	1.0	4
Cr	8.9	25	1.3
Cs	>0.19	-	-
Eu	0.97	-	-
Fe	1130	2200	6
Hf	>0.2	-	-
I	>9	<4	1.3
K	580	870	2.5
La	1.1	2.4	4.7
Mg	-	1400	7
Mn	41	75	2.4
Na	970	650	4
Pb	190	970	0.7
Sb	1.2	6.9	1.2
Sc	0.19	0.27	6
Se	>2	-	-
Sm	0.09	0.33	6.5
Th	>0.5	-	-
Ti	80	170	6
V	4.3	14	0.9
Zn	78	320	1.2

One measure still widely used is total suspended particulate (TSP). It is a mass concentration measure of all particles that are suspended in the air without regard to size. Two similar common measures of PME are the PM_{10} and $PM_{2.5}$ concentration. These are mass concentrations of particulate matter that are of a median aerodynamic diameter of less than 10 μm or less than 2.5 μm, respectively. Since these only measure particles that can penetrate beyond the extrathoracic region, they are believed to be more relevant to health effects. Furthermore, they are relevant to the bimodal distribution of particles in ambient air as well. Since the low or saddle point which distinguishes the two modes of atmospheric aerosols is in the range of 1 to 3 μm, the conventional division between the coarse and fine modes is 2.5 μm. Thus PM_{10} is a particle measurement relevant to human health effects that includes the coarse and fine modes, and $PM_{2.5}$ is a particle measurement relevant to human health effects that includes only the fine mode.

Also common are mass concentration measures of specific components of the particulate matter mix, such as H_2SO_4, SO_4^{2-}, and H^+. Less common measures include the number of particles of a specific median aerodynamic diameter per unit volume.

Sources

Transportation, mining operations, thermal power generation plants, waste incinerators, construction, smelting, and processing are major sources of particulate matter in Ontario.[1,12] The breakdown of PM_{10} emission sources in Ontario can be found in Table 2-2.[12]

Table 2-2. Ontario PM_{10} emission sources by sector

Sector	**Percentage of total (not including emissions from road dust, construction, agriculture, etc.)**
Area fuel combustion	14
Transportation	11
Smelters/primary metal industry	9
Pulp and paper industry	8
Other industrial processes	17
Miscellaneous area sources	41

Exposure and exposure standards

Table 2-3 [12] lists the national and Ontario standards for total suspended particulate matter, which includes PM_{10}, and the proposed Ontario standard for PM_{10}.[1,13,14] Despite a 54 per cent decline in national total suspended particulate levels in the 1974-1992 period, as indicated in Table 2-4, particulate matter remains an important factor in determining air quality, due to the significant concentrations which are still present, especially as compared to other major pollutants.[1] In Ontario, over 300,000 tonnes of particulate matter were emitted from transportation, utilities, and major industrial processes in 1995.[12] For PM_{10}, the arithmetic mean concentration in Ontario was 21.5 $\mu g/m^3$ in 1995.[12] The five-year (1991 to 1995 inclusive) trend in annual PM_{10} concentration in Ontario was stable, ranging from 21.2 to 25.2 $\mu g/m^3$.[12] The annual arithmetic mean concentration for the Toronto monitoring site for 1995 was 23 $\mu g/m^3$.[12]

Table 2-3. Canadian and Ontario air quality standards for particulate matter

Standard	$\mu g/m^3$ (average)
National - 24 hour acceptable level, total suspended particulate	120
National - annual acceptable level, total suspended particulate	70
Provincial - 24 hour ambient air quality criterion, total suspended particulate	120
Provinical - annual ambient air quality criterion, total suspended particulate	60 (geometric mean)
Provincial - 24 hour ambient air quality criterion, PM10 (Interim standard, proposed May 21, 1997)	50

Table 2-4. Canadian air quality trends -- Data summary (percentage of national annual maximum acceptable level,(*) = not monitored)

Year	TSP	CO (8 hour)	SO2	NO2	O3 (1 hour)	Lead
1974	112	47	56	(*)	(*)	100
1975	94	43	47	N/A	(*)	81
1976	94	34	52	N/A	(*)	72
1977	88	34	47	58	(*)	68
1978	88	32	43	55	(*)	62
1979	94	35	43	49	109	57
1980	96	32	39	47	105	50
1981	84	35	35	43	102	47
1982	74	32	35	43	99	40
1983	66	27	30	45	98	34

Table 2-4 (cont'd). Canadian air quality trends – Data summary (percentage of national annual maximum acceptable level,(*) = not monitored)

1985	61	26	26	42	93	26
1986	61	26	26	42	90	24
1987	68	24	22	40	90	15
1988	62	22	26	40	113	9
1989	62	21	27	42	98	7
1990	63	19	27	39	90	3
1991	55	18	20	38	86	3
1992	50	15	22	34	73	3

Defences

Particles of the size, composition, and concentration described above may be deposited in the human respiratory tract according to the model presented. Once deposited, various respiratory defence mechanisms may interact with the particulate matter, including: [15]

1. the mucociliary escalator.
2. reflexes such as coughing and sneezing.
3. phagocytosis by lung macrophages.
4. dissolution.
5. the inflammatory response.
6. the cell-mediated immune response.

Despite these defences, and perhaps as a result of their activation, exposure to fine particulate matter is suspected of having a host of cardiopulmonary effects. It has been associated with premature mortality, aggravation of respiratory and cardiovascular disease, changes in lung function, increased respiratory symptoms, changes to lung tissue and structure, and altered respiratory defence mechanisms.[3,9,16,17]

Epidemiological studies on the respiratory health effects of particulate matter

The majority of the evidence for the respiratory health effects from respirable particulate matter comes from epidemiological studies. Statistically significant associations have been found between various measures of particulate matter exposure, including TSP, BS, CoH, PM_{10} and $PM_{2.5}$, and various measures of mortality and morbidity, including respiratory mortality,

cardiorespiratory mortality, total mortality, hospital admissions for respiratory illness, school absences in children, and total emergency room visits.[3,9,17] Many types of studies have been undertaken, using different methods and measures of variables and outcomes.[16]

Acute exposure and mortality

The U.S. Environmental Protection Agency has concluded that there is convincing evidence for associations between daily mortality and 24-hour concentrations of PM, despite variations in location, modelling approaches, adjustment for covariates, etc.[9,17] Relative risks for total non-accidental mortality have ranged from 1.015 to 1.085 for an increase of 50 $\mu g/m^3$ PM_{10}. More limited evidence suggests that particles in the fine size range (<2.5 μm) may be responsible for the effects.[17]

The American Thoracic Society Committee of the Environmental and Occupational Health Assembly (CEOHA) chaired by Rebecca Bascom reported that total daily mortality, and especially respiratory mortality and cardiovascular mortality, has been associated with various measures of particulate matter exposure, including British smoke, coefficient of haze, total suspended particulate, and PM_{10}. It was suggested that acid concentration may be the true correlate, but this has not been confirmed.[3]

In general, increases of 1 to 8% in the daily mortality rate have been found in most epidemiological studies of short-term exposure to PM.[16] Dockery and Pope estimated that a 10 $\mu g/m^3$ increase in PM_{10} was generally associated with a 1% increase in total mortality, a 3.4% increase in respiratory mortality, and a 1.4% increase in cardiovascular mortality.[18]

Some recent studies analyzing the relationship between acute particulate matter exposure and mortality are summarized in Table 2-5. These studies confirm that numerous measures of particulate matter exposure, including BS, CoH, TSP, PM_{10}, $PM_{2.5}$, and SO_4^{2-}, are associated with various measures of non-accidental mortality, especially respiratory and cardiovascular mortality, and especially during the summer months. Increases of 100 $\mu g/m^3$ PM_{10} have been associated with increases in daily mortality ranging from 4 to 16%. Populations at greatest risk appear to be the elderly, the very young, and those with existing respiratory and cardiac conditions.

Table 2-5. Epidemiological studies of particulate matter exposure and mortality

Investigators	Details	Findings
Schwartz and Dockery (1992) [19]	Study of particulate air pollution in Steubenville, Ohio	Total suspended particulate associated with daily mortality
Wietlisbach and Pope (1996) [20]	Study of air pollution in three Swiss cities	TSP associated with daily mortality
Borja-Aburto et al. (1997) [21]	Study of air pollution in Mexico City	Total suspended particulate concentrations associated with daily mortality, independent of other pollutants
Wordley et al. (1997) [22]	Study of particulate pollution in Britain	Total mortality and mortality due to circulatory diseases and COPD were positively associated with levels of PM_{10} on the same day and 24 hours previously
Schwartz (1990-1) [23]	Synthesis of studies in the U.S. and London	Calculated a 1% increase in total daily mortality, a 3.4% increase in respiratory mortality, and a 1.8% increase in cardiovascular mortality associated with a 10 $\mu g/m^3$ increase in PM_{10}
Dockery et al. (1992) [24]	The associations between total daily mortality and various measures of particulate and gaseous air pollution were investigated in St. Louis and eastern Tennessee.	Associations were found for PM_{10}, and weaker ones for $PM_{2.5}$, sulfate, and aerosol acidity. Associations with gaseous pollutants were not significant.
Pope et al. (1992) [25]	Study of PM_{10} in the Utah Valley	A five-day mean PM_{10} increase of 100 $\mu g/m^3$ associated with a 16% increase in deaths per day
Saldiva et al. (1995) [26]	Daily mortality of people 65 years and older and air pollution levels were studied in Sao Paulo, Brazil	An increase in PM_{10} of 100 $\mu g/m^3$ was associated with an 13% increase in overall mortality, with a linear dose response relationship.
Dab et al. (1996) [27]	Study of air pollution in Paris	PM_{13} associated with a 17% increase in the risk of respiratory death
Ito and Thurston (1996) [28]	Study of PM_{10} and various subpopulations in the U.S.	PM_{10} and O_3 both significantly associated with same-day and next-day non-accidental mortality, and the highest association was among the sub-population of African-American women

Table 2-5 (cont'd). Epidemiological studies of particulate matter exposure and mortality

Investigators	Details	Findings
Pope (1996) [29]	Study of particulate air pollution in the Utah Valley	PM_{10} associated with increased mortality, especially respiratory and cardiovascular mortality, while levels of SO_2, O_3, and acidity were low
Verhoeff et al. (1996) [30]	Study of air pollution in Amsterdam	Relative risk of daily mortality for a 100 $\mu g/m^3$ increase in black smoke on the same day was 1.19, and for PM_{10}, 1.06. This risk was independent of other pollutants, and was higher for people over 64
Katsouyanni et al. (1997)[31]	Study of SO_2 and particulate matter exposure in 12 European cities	Calculated a 3% increase in daily mortality associated with a 50 $\mu g/m^3$ increase in black smoke, and a 2% increase for PM_{10}
Woodruff et al. (1997) [32]	Cohort study of 4 million infants born between 1989 and 1991. Associations were examined between cause-specific mortality and categories of high, medium or low PM_{10} exposure.	Odds ratio for total postneonatal mortality for the high versus low exposure groups was 1.10. High PM_{10} exposure was associated with respiratory causes (OR=1.40) and SIDS (OR=1.26) in normal birth weight infants.
Schwartz and Marcus (1990) [33]	Study of air pollution episodes in London between 1958 and 1972	British smoke associated with excess mortality, even after controlling for SO_2 as a co-pollutant
Zmirou et al. (1998) [34]	Time-series analysis of mortality and air pollution from 10 large European cities	RR of death from cardiovascular conditions was 1.02 for a 50 $\mu g/m^3$ increase in BS, and RR of death from respiratory diseases was 1.05.
Glasser and Greenburg (1971) [35]	Study of air pollution episodes in New York City between 1960 and 1964	Coefficient of haze associated with daily total mortality, especially respiratory and cardiovascular
Ostro (1995) [36]	The association between airport visibility data (estimating $PM_{2.5}$ concentration) and mortality was investigated in southern California between 1980 and 1986.	There was a small but statistically significant association between estimated fine particles and total mortality and respiratory mortality in the summer quarters, but not for the year as a whole.
Pope and Kalkstein (1996) [37]	Study of particulate air pollution in the U.S.	Particulate pollution consistently accounts for a proportion of increased mortality even after different models of weather patterns are used to account for potentially confounding weather variables

Chronic exposure and mortality

Two well-designed cohort studies on the health effects of chronic particulate matter exposure have been undertaken. In one, measurements were taken in six eastern U.S. cities for eight years, and aerosol acidity concentrations were measured for approximately one year. PM_{10}, $PM_{2.5}$, and SO_4^{2-} were each significantly associated with increased daily mortality. The strongest association was found with $PM_{2.5}$. A 10 $\mu g/m^3$ increase in two-day mean $PM_{2.5}$ was associated with a 1.5% increase in total daily mortality. Larger increases were found for deaths caused by chronic obstructive pulmonary disease (+3.3%) and by ischemic heart disease (+2.1%). The increase in relative risk reported between the cities with the highest and lowest PM concentrations was 26% for total mortality, and 37% for cardiopulmonary mortality.[38]

In the other study, 552,138 subjects were followed for seven years. Multi-year concentrations of $PM_{2.5}$ and sulphate were found to be associated with total and cardiopulmonary mortality. A 17% increased risk for total mortality and a 31% increased risk for cardiopulmonary mortality was reported.[39]

Acute exposure and morbidity

The U.S. Environmental Protection Agency has concluded that studies of particulate air pollution have demonstrated small but significant positive relationships with morbidity outcomes such as hospitalization for COPD, pneumonia, and other respiratory illnesses, especially in elderly patients, lower respiratory disease and cough, decreased peak flow in children, and decreased FEV_1 in adults. It could not be concluded that fine particles (< $PM_{2.5}$ μm) were better predictors of morbidity, mostly due to the high correlations among different particle concentration measurements.[9,17]

The CEOHA review identified the following associations between measures of morbidity and exposure: hospital admissions of children for respiratory illness (with PM_{10}), total emergency room visits (with TSP), emergency room admissions for COPD (with British smoke), admission for acute respiratory disease problems (with total sulphates), total hospital admissions (with peak H^+ concentration), hospital admissions for asthma and total respiratory admissions (with sulphate and H^+), lower respiratory symptoms in school children (with PM_{10}), upper and lower respiratory symptoms in winter (with PM_{10}), cough in children (with PM_{10}), reduction in

FVC in children (with TSP), decreased peak flow in children (with PM_{10} in winter), increased incidence of respiratory symptoms in children (with PM_{10} in winter), cough and shortness of breath in asthmatic adults (with $PM_{2.5}$ and H^+), increased asthma medication use in asthmatics (with PM_{10}), change in pulmonary function in smokers with COPD symptoms (with PM_{10}), increased emergency room admissions for COPD (with Black smoke), and increases in work-loss days, restricted activity days, and respiratory-related restricted activity days (with estimates of fine particle exposure based on airport visibility data).[3]

Dockery and Pope estimated that a 10 $\mu g/m^3$ increase in PM_{10} exposure was generally associated with a 1% increase in hospital admissions and emergency room visits for all respiratory complaints, a 2.3% increase for asthma specifically, a 3% increase in the exacerbation of asthma and lower respiratory symptoms, and a 0.1% decrease in lung function.[18]

Some recent studies analyzing the relationship between acute particulate matter exposure and morbidity are summarized in Table 2-6. These studies indicate that increases in a variety of exposure measurements, including TSP, BS, PM_{10}, $PM_{2.5}$, sulphates, and H^+, have been associated with a variety of morbidity outcome measurements, including hospital visits for respiratory and cardiac problems, increased frequency of respiratory tract illness, increased severity and frequency of respiratory symptoms, decreased lung function parameters, increased asthma medication use, and increased school absences. These morbidity outcomes affected the general population, but especially elderly patients with respiratory problems, and children with asthma. The effects were also more often seen during the summer months.

Chronic exposure and morbidity

The EPA has suggested that evidence exists for a role of chronic exposure to particulate matter in causing lung function decrements in adults and various respiratory effects in children.[9,17] The CEOHA review cited evidence for associations between reports of bronchitis, chronic cough, and lower respiratory illness in school children and aerosol acidity, chronic respiratory symptoms or illnesses and TSP, symptoms of COPD and cumulative TSP exposure, and increased mortality, especially cardiopulmonary mortality, and $PM_{2.5}$.[3]

Table 2-6. Epidemiological studies of particulate matter exposure and morbidity

Investigators	Details	Results
Burnett et al. (1994) [40]	Daily respiratory admissions to 168 hospitals in Ontario were related to estimates of exposure to O_3 and sulfates in the vicinity of each hospital	Positive statistically significant associations were found for hospital admissions in the summer and both O_3 and sulfate levels recorded on the day of admission and up to 3 days prior to admission. The combination of O_3 and sulfates was found to be associated with admissions for asthma, COPD, and infections; associations were found for each age group, especially infants. No associations were found with non-respiratory admissions or admissions in the winter.
Burnett et al. (1995) [41]	Hospital admissions for cardiac and respiratory disease were compared to daily measures of particulate sulphate concentration over a six year period	A 13 $\mu g/m^3$ increase in sulphates the day prior to admission was associated with a 3.7% increase in respiratory admissions and a 2.8% increase in cardiac admissions. Similar results were obtained for non-summer months when ambient temperature and ozone concentration were considered in the model. Admissions for cardiac disease in elderly patients only (>65) was more strongly associated with particulate sulphate concentration (3.5%)
Schwartz (1995) [42]	Hospital admissions for respiratory disease in two cities with similar particle levels but different SO_2 levels were studied	RR's of 1.06 and 1.10 were calculated for a 50 $\mu g/m^3$ increase in PM_{10}, little changed by controlling for O_3 or SO_2.
Xu et al. (1995) [43]	Hospital records and air pollution levels were studied in Beijing, China	Both SO_2 and TSP were found to be significant , independent predictors of hospital outpatient visits to the internal medicine department.
Dab et al. (1996) [44]	Study of air pollution and respiratory health outcomes	PM_{13} and black smoke associated with hospital admissions due to all respiratory diseases
Gordian et al. (1996) [45]	Study of PM_{10} and medical visits in Alaska	An increase of 10 $\mu g/m^3$ in PM_{10} associated with a 3-6% increase in visits for asthma and a 1-3% increase in visits for upper respiratory diseases

Table 2-6 (cont'd). Epidemiological studies of particulate matter exposure and morbidity

Investigators	Details	Results
Schwartz (1996) [46]	Study of particulate pollution and hospital admissions in Spokane	PM_{10} associated with increased risk of hospital admission for respiratory illness. PM_{10} and SO_2 levels are not correlated in this city
Tanaka et al. (1996) [47]	Hospital visits for asthma symptoms of 102 patients were compared with meteorological conditions	There was an 8.8% increase in visits for asthma symptoms on low water vapour pressure acid fog days.
Anderson et al. (1997) [48]	Study of air pollution and hospital admissions in six European cities	The relative risk for a 50 $\mu g/m^3$ increase in daily mean level (lagged 1-3 days) of black smoke was 1.04 and of TSP was 1.02
Burnett et al. (1997) [49]	Hospital admissions for cardiac disease and respiratory disease was compared to daily measures of air pollutants for 3 consecutive summers	Particle mass and composition (sulphates, acidity) could not be considered independent risk factors for cardiorespiratory disease exacerbation as measured by hospital admission.
Choudhury et al. (1997) [50]	Study of PM_{10} and medical visits in Alaska	PM_{10} associated with visits for asthma, bronchitis, and upper respiratory infections. The relative risk was higher on warmer days
Delfino et al. (1997) [51]	Study of air pollution and emergency room visits for respiratory illnesses in Montreal	One hour maximum O_3, PM_{10}, $PM_{2.5}$, and SO_4^{2-} were associated with respiratory visits for patients over 64 years of age. Relative mass effects were $PM_{2.5}>PM_{10}>SO_4^{2-}$
Schwartz (1997) [52]	Study of particulate pollution and hospital admissions in Tuscon	A 23 $\mu g/m^3$ increase in PM_{10} was associated with a 2.75% increase in the risk of cardiovascular hospital admissions in the winter. PM_{10} is the only significant pollutant in Tuscon in the winter months
Wordley et al. (1997) [53]	Study of particulate pollution in Britain	PM_{10} on the same day associated with respiratory admissions, cerebrovascular admissions, and bronchitis admissions Mean PM_{10} for the previous three days associated with pneumonia, respiratory admissions, and asthma admissions

Table 2-6 (cont'd). Epidemiological studies of particulate matter exposure and morbidity

Investigators	Details	Results
Delfino et al. (1998) [54]	Daily ER visits for respiratory ilnesses and outdoor air pollution levels were compared for 25 hospitals in Montreal for the period June to August, 1989-1990	An association between respiratory ER visits for the elderly (65+) and estimated $PM_{2.5}$ lagged one day was confounded by temperature and O_3 levels. One-day lagged 1 and 8 hr. maximum O_3 concentrations and respiratory ER visits for elderly patients were significantly associated for the summer of 1989.
Ostro et al. (1991) [55]	Panel study of 207 asthmatics in Denver in the winter of 1987-88	Airborne H^+ and fine particulate matter were significantly associated with moderate or severe cough; H^+ and sulfates were significantly associated with shortness of breath
Schwartz et al. (1994) [56]	Reported respiratory symptoms of 1844 children were compared with ambient air pollution levels during the summer months	Associations were found between PM_{10} and incidence of cough and lower respiratory symptoms, and a less strong association with upper respiratory symptoms was also found. Other measures ($PM_{2.5}$, light scattering, sulfate particles, aerosol strong acidity) were not more strongly associated with reported symptoms
Pope (1996) [57]	Study of air pollution and respiratory health outcomes in the Utah Valley	PM_{10} and increased incidence of respiratory symptoms, decreased lung function, increased school absenteeism, increased respiratory hospital admissions, and increased mortality, especially respiratory and cardiovascular mortality
Gielen et al. (1997) [58]	61 children, 77% of whom were taking asthma medication, were followed in the summer of 1995	Black smoke in particular was associated with acute respiratory symptoms and asthma medication use; weaker associations were found for PM_{10} and O_3.
Harre et al. (1997) [59]	40 subjects with COPD were followed for 3 months during the winter of 1994	An increase in PM_{10} equal to the interquartile range was associated with an increase in nighttime chest symptoms; a similar rise in NO_2 was associated with increased inhaler use.

Table 2-6 (cont'd). Epidemiological studies of particulate matter exposure and morbidity

Investigators	Details	Results
Peters et al. (1997) [60]	Study of particulate air pollution and asthmatic children in Eastern Europe	Exposure to particulate SO_4^{2-} associated with decreased peak flow, increased respiratory symptoms, increased school absences, increased fever, and increased medication use
Peters et al. (1997) [61]	31 children who took asthma medication and 51 who took no medication were studied	5 day mean concentrations of sulphate particles less than 2.5 μm in diameter were weakly associated with respiratory symptoms in nonmedicated children, and were associated with increased medication use in the other children, as well as decreased peak flow and increased cough (despite the medication).
Stern et al. (1989) [62]	Cross-sectional study of children from two rural Canadian communities, one with low pollution, one with moderate levels.	The community with moderate pollution had higher SO_2, sulfate, and particulate nitrate levels, and the children from that community had significantly lower levels for FVC and FEV_1, even when children with respiratory symptoms were excluded.
Koenig et al. (1993) [63]	Study of particulate pollution from wood-burning sources and asthmatic children	Calculated a drop of 34 and 37 ml in FEV_1 and FVC associated with an increase in $PM_{2.5}$ of 20 $\mu g/m^3$
Stern et al. (1994) [64]	Cross-sectional study of pre-adolescent school children from 10 rural Canadian communities, 5 with low pollutant exposure, 5 with moderate	There were significant differences in annual mean 1 hr. maximum O_3 concentration and annual mean concentration of inhalable sulfates between the 2 sets of communities. Children in the more polluted communities had lower FVC and FEV_1. There were no other significantly different results (flow parameters, symptoms).
Neas et al. (1995) [65]	83 children from Uniontown PA were studied during the summer	Children who were reported as symptomatic by questionnaire also showed a decrease in peak flow rate and increase in cough associated with an increase in particle strong acidity

Table 2-6 (cont'd). Epidemiological studies of particulate matter exposure and morbidity

Investigators	Details	Results
Neas et al. (1995) [66]	83 children from Pennsylvania were studied during the summer of 1990	An increase in particle-strong acidity was associated with a decrease in PEF and an increased incidence of cough. Increased O_3 was also associated with decreased PEF
Studnicka et al. (1995) [67]	Panel studies of summer camp children in the Austrian Alps	In children exposed to higher than normal levels of acidic particles, a significant decrease in FEV_1 of 0.99 ml per nmol/m^3 H+ was reported
Linn et al. (1996) [68]	Study of school children from three S. California communities with different air quality	Morning FVC decreased with increased PM or NO_2. Morning to afternoon change in FEV_1 became more negative with increasing PM, NO_2, or O_3. All changes were slight (<2% predicted change from high to low pollution day)
Neas et al. (1996) [69]	108 children were studied over one summer	Fungal spore concentrations were associated with a decrease in morning peak flow and morning cough, and not associated with respirable particle mass. Particle strong acidity and respirable particle concentration were associated with decreased evening peak flow and increased cold or cough episodes
Raizenne et al. (1996) [70]	Study of acid aerosol exposure and children's health in 24 communities in Canada and the U.S.	Calculated a 52 nmol/m^3 difference in annual mean particle strong acidity associated with a 3.5% decrease in adjusted FVC and a 3.1% decrease in adjusted FEV_1. The relative odds for low lung function was 2.5 across the range of particle strong acidity exposures
Romieu et al. (1996) [71]	Panel study of 71 children with mild asthma living in Mexico City	Decreased peak flow, increased respiratory symptoms, increased lower respiratory illness were each associated with PM_{10} levels
Scarlett et al. (1996) [72]	154 children were studied for 2 months in the summer of 1994	There was a small but significant inverse relationship between one-day lagged PM_{10} concentration and FVC. No other significant relationships were seen (with other pollutants or other lung function measures)

Table 2-6 (cont'd). Epidemiological studies of particulate matter exposure and morbidity

Investigators	Details	Results
Pekkanen et al. (1997) [73]	39 asthmatic children were followed for 57 days, and PEF measured, as well as PM_{10}, BS, and particle number concentrations in size classes from 0.01 to 10.0 μm	Declines in morning PEF were most closely associated with PM_{10} and BS, rather than measures of ultrafine particle number concentrations
Peters et al. (1997) [74]	27 nonsmoking asthmatic adults were followed during the winter of 1991-92	The fine (0.1-0.5 μm) and ultrafine (<0.1 μm) fractions of particles were associated with decreased PEF, increased cough, and increased ill feelings. The effects of the number of ultrafine particles was greatest.
Timonen and Pekkanen (1997) [75]	74 children with asthma and 95 children with cough only, were followed for 3 months	PM_{10}, BS, and NO_2 were each assocated with declines in morning PEF among asthmatic children. In addition, a significant association between SO_2 and morning and evening PEF and the incidence of upper respiratory symptoms was found among children with cough living in urban areas.
Vedal et al. (1998) [76]	A potentially sensitive subgroup of children from a pulp mill community on Vancouver Island were followed for 18 months	For all the children studied, increases in PM_{10} were correlated with declines in PEF and increased reporting of cough, phlegm production, and sore throat. Only the subgroup of children with diagnosed asthma showed consistent effects: decreased PEF and increased reported cough with increased PM_{10}.
Souza et al. (1998) [77]	Histopathological examination of lung tissue samples from humans who died from violent causes, and who lived either in area of high levels of inhalable particles or in cities with agrarian economies	Lung tissue samples from individuals who lived in the high pollution area had more damage than the control group, suggesting that particle exposure may contribute to the pathogenesis of airway disease.

Recent studies of chronic exposure have found similar associations. One study calculated that an increase in annual mean TSP concentration of 100 $\mu g/m^3$ was associated with an 80% relative increase in the odds of reporting emphysema, chronic bronchitis, or asthma.[78]

An American study of several communities found that children living in the community with the highest levels of particle strong acidity were significantly more likely to report at least one episode of bronchitis in the past year compared to children living in the least-polluted community. Fine particulate sulphate was also associated with higher reporting of bronchitis.[79]

A European study of long-term exposure to air pollution found that a 10 $\mu g/m^3$ increase in PM_{10} was associated with a 3.4% decrease in FVC, indicating a decline in lung function which could predispose towards a disease state.[80]

A ten year study of a nonsmoking population living in the vicinity of nine airports throughout California, found that long-term ambient concentrations of estimated $PM_{2.5}$ in excess of 20 $\mu g/m^3$ were found to be associated with the development of definite symptoms of chronic bronchitis. Estimated mean concentrations of $PM_{2.5}$ were also associated with increasing severity of respiratory symptoms related to general airway obstructive disease, chronic bronchitis, and asthma, but it could not be concluded that this was due to $PM_{2.5}$ exposure.[81]

A similar analysis found that elevated levels of one or more of TSP, PM_{10}, $PM_{2.5}$, and suspended sulfates, were associated with the following disease outcomes: incidence of myocardial infarction, and development of symptoms or increasing severity of existing symptoms related to airway obstructive disease, chronic bronchitis, and asthma.[82]

Animal and cell studies on the respiratory health effects of particulate matter

Most animal and cell studies use prolonged exposure periods at high concentrations, making extrapolation to humans exposed to the ambient environment difficult. In addition, as with the epidemiological data, the animal and cell data varies with respect to particle size, composition, and concentration, duration of exposure, measured responses, and other environmental conditions. However, the information collected is still valuable.

Acute functional responses to H_2SO_4 aerosol exposure observed in animal studies include bronchoconstriction, increased airway resistance, decreased compliance, transient alteration in

the distribution of ventilation, increased respiratory rate, and decreased clearance (nasal, tracheal, and bronchial) due to ciliary dysfunction. Other acute responses include alveolar injury and tracheal injury. Exposure has also been shown to alter lung defense mechanisms and resistance to bacterial infection. Responses to chronic exposure include bronchiolar epithelial hyperplasia, thickening of the walls of the respiratory bronchioles, altered distribution of ventilation, altered mucociliary clearance, decreased lung function (DLCO, RV, TLC, IC, and FRC), reduced compliance, and increased resistance. Despite this evidence, in many other studies, no effects (acute and/or chronic) were seen. [9,17,83]

Studies also suggest that metal aerosols, such as those containing Cd or Ni, impair the bacterial defences of the lung by their direct toxicity to alveolar macrophages (reducing their phagocytotic ability), by slowing clearance, by inhibiting antibody-dependent aggregation reactions, and possibly by depressing antibody production, thus increasing the susceptibility of some species to airborne infectious diseases. They may also contribute to lung damage by triggering inflammatory responses.[9,17]

Further research into the respiratory effects of particulate matter exposure in animals and in vitro has often found measurable responses to exposure. Tables 2-7 and 2-8 summarize some of these studies. They indicate that exposures to particulate matter such as PM_{10}, concentrated ambient particles (CAP), fly ash, H_2SO_4, SO_4^{2-}, metals, and diesel exhaust particles, can cause changes in pulmonary function, inflammation, tissue injury, decreased lung defence functioning, and the release of reactive oxygen species. Recent research has also found that PM_{10} has substantial free radical activity on its surface, providing a possible mechanism as to how it can induce oxidant stress, leading to inflammation and damage.[84]

Many, but not all, studies of specific components of particulate air pollution, especially diesel exhaust particles, have found evidence for carcinogenic potential. [85,86,87,88,89] Whether or not particulate matter is carcinogenic to humans is a question which needs further research. Some research also indicates that particulate pollution may act as an adjuvant to allergens which can trigger and exacerbate or perhaps even cause allergic airway disease.[90,91,92,93,94] Again, further research is required to confirm this potential mechanism whereby PME could exacerbate asthma or allergy.

Table 2-7. Animal studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Conner et al. (1985)[95]	Animal/guinea pigs	3 hr exposure to 6 mg/m^3 of submicron zinc oxide particles (CMD = 0.05 μm) mixed with 1 ppm SO_2, on 6 consecutive days	Exposure caused increased lung weight and inflammation of proximal alveolar duct, resolved by 72 hours post exposure. TLC, VC, FRC, alveolar volume and DLCO were decreased following exposure and had not resolved by 72 hours post-exposure
Lam et al. (1985) [96]	Animal/guinea pigs	5 mg/m^3 ZnO particles (0.05 μm) 6 days exposure @ 3 hours/day	Decreased VC, FRC, alveolar volume, and DLCO following last exposure Transient decrease in compliance and in TLC Increase in lung weights suggestive of inflammation
Wiester et al. (1985) [97]	Animal/guinea pigs	904 mg/m^3 Mt. St. Helens fine volcanic ash 2 hours exposure	No change in pulmonary function Decreased responsiveness to histamine Extensive particle phagocytosis by macrophages
Wehner et al. (1986) [98]	Animal/rats	5 mg/m^3 Mt. St. Helens volcanic ash 50 mg/m^3 Mt. St. Helens volcanic ash 50 mg/m^3 quartz Exposure duration: 24 months @ 6 hours/day, 5 days/week	Increased respiratory frequency, alveolar macrophage accumulation, interstitial reaction, lympho-reticular reaction, alveolar proteinosis, and some epermoid carcinomas in all exposed groups. The ash-exposed group displayed a lesser degree of damage
Chen et al. (1987)[99]	Animal/guinea pigs	Exposed for 1 hour to sodium sulfite aerosols (MMAD = 0.36 μm) of SO_3^{2-} concentrations of 474, 669, and 972 μg/m^3. Exposed for 1 hour to concentrations of 0, 204, 395, and 1152 μg/m^3.	Dose-related increased in resistance and decreased in compliance were observed in unanaesthetized animals. Dose-related decreases in TLC, VC, FRC, RV, and DLCO, and increases in wet lung weights, were observed with increasing exposure in anaesthetized, tracheotomized animals.

Table 2-7 (cont'd). Animal studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Chen et al. (1990) [100]	Animal/guinea pigs	5.8 mg/m^3 Illinois no. 6 ultrafine coal fly ash (0.21 μm, high sulphate content) or Montana lignite fly ash (alkaline)	Decrease in TLC, VC, and DLCO following exposure to Illinois no. 6 fly ash, not Montana fly ash.
Mannix et al. (1982)[101]	Animal/rats	5 ppm SO_2 1.5 mg/m^3 sulphate aerosol 4 hours exposure	No changes in nasopharyngeal or parenchymal clearance rates
Loscutoff et al. (1985) [102]	Animal/guinea pigs and rats	1 mg/m^3 $(NH_4)_2SO_4$ or 1 mg/m^3 NH_4NO_3 aerosols Exposure duration: 5 or 20 days @ 6 hours/day (5 days/week)	Guinea pigs pretreated with elastase showed no effects of exposure Rats pretreated with elastase displayed pulmonary emphysema after exposure Rats exposed to NH_4NO_3 showed no consistent effect Rats exposed to $(NH_4)_2SO_4$ showed increased RV and FRC, and decreased nitrogen washout
Strom et al. (1990)[103]	Animal/rats	50 mg/m^3 diesel exhaust particles Exposure duration: 52 weeks @ 20 hours/day, 7 days/week	52 weeks after end of exposure, 80% of deposited particles had been eliminated
Kitabatake et al. (1991) [104]	Animal/guinea pigs	Animals were expsed to ammonium sulfate aerosols at concentrations of 0.2, 0.4, and 2.0 mg/m^3, and to 0.2 mg/m^3 aerosol plus 0.1 ppm SO_2, for 2 hours per day. 30 minutes post-exposure, they were exposed to a mixture of bovine serum and egg albumin to induce asthmatic dyspnea. Following these tests, the animals were exposed to acetylcholine.	Body plethysmography revealed increased dyspnea after exposure to aerosol (dose-dependent). Sensitivity to acetylcholine was increased after exposure to 0.4 and 2.0 mg/m^3 ammonium sulfate aerosol.
Last et al. (1986) [105]	Animal/rats	0.64 ppm O_3 and 1 mg/m^3 H_2SO_4 (0.5 μm) control: O_3 and $(Na)_2SO_4$ or NaCl	Synergistic interaction of O_3 and H_2SO_4 on indicators of inflammation; no such interaction with neutral aerosols

Table 2-7 (cont'd). Animal studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Last (1991) [106]	Animal/rats	0.12 ppm O_3 and 5-20 $\mu g/m^3$ H_2SO_4 1-9 days exposure	Synergistic interaction of O_3 and H_2SO_4 on indicators of inflammation and injury
Li et al. (1996) [107]	Animal/rats	PM_{10}	BAL fluid showed an increase in neutrophils and in LDH, and a decrease in GSH Epithelial permeability increased
Warheit et al. (1996) [108]	Animal/rats	TiO_2 or carbonyl iron particles 4 weeks exposure	Sustained pulmonary inflammation and impaired particle clearance
Dreher et al. (1997)[109]	Animal/ rats	Intra-tracheal instillation of ROFA suspension, ROFA leachate containing Fe, V, Ni, Ca, Mg, and sulfate, leachate depleted of Fe, V, and Ni, and a solution containing Fe, V, and Ni.	BAL fluid recovered indicated severe inflammation following ROFA instillation. Similar results were obtained with other preparations containing soluble transition metals, and minimal injury without.
Dye et al. (1997) [110]	Cell/rat tracheal epithelial cells Animal/rats	Rats were intra-tracheally instilled with ROFA (500 µg per rat)	Animal exposure caused pulmonary neutrophilic inflammation, which was reduced by administration of DMTU.
Godleski (1997) [111]	Animal and cell/ various species	concentrated ambient particles	Animals with pre-existing pulmonary inflammation demonstrated increased mortality Health animals demonstrated no significant effects Significant cardiac electrophysiologic alterations were found in healthy and diseased animals
Kadiiska et al. (1997) [112]	Animal/rats	500 $\mu g/m^3$ oil fly ash or saline	Analysis of lung tissue demonstrated free radical production, apparently associated with soluble metals in the ash (vanadium, nickel, and iron sulfates)
Kodavanti et al. (1997) [113]	Animal/rats	residual oil fly ash	Some strains demonstrated inflammation, alveolar, airway, and interstitial thickening, and/or focal alveolar fibrosis

Table 2-7 (cont'd). Animal studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Li et al. (1997) [114]	Animal/rat	Intratracheal instillations of PM_{10}, followed by BAL 6 hours later	Influx of neutrophils, increased epthelial permeability, increased lactate dehydrogenase concentrations, decreased GSH, leukocytes produced greater amounts of NO and TNF-alpha
Vincent et al. (1997) [115]	Animal/rat	4 hour exposure to clean air, 0.8 ppm O_3 , urban dust EHC-93 at 5 or 50 mg/m^3 concentrations, or O_3 + EHC-93; 32 hours later, proliferating cells labelled and lungs fixed	EHC-93 alone did not increase labelling; O_3 alone did; the effects of O_3 were potentiated by low or high concentrations of EHC-93; effects were most pronounced in terminal bronchial epithelia and alveolar ducts
Ghio et al. (1998)[116]	Animal/rats	Oil fly ash instillation	24 hours post exposure, levels of ferritin, lactoferrin, and transferrin were maximall increased, possibly to control metal-induced oxidative stress
Vanda et al. (1998)[117]	Animal/dogs	BAL was performed from dogs from different areas of Mexico City, and from a rural area	The BAL fluid with the highest levels of neutrophils were from dogs from the area with the highest O_3; that with the highest levels of ferruginous bodies were from dogs from the area with the highest levels of PM
Juhos et al. (1978)[118]	Animal/rats	3 conditions: 2 mg/m^3 H_2SO_4 (0.3 μm) H_2SO_4 plus 0.9 ppm O_3 O_3 alone Exposure duration: 82 days @ 8 hours/day	Slight morphological injury to the respiratory tract following aerosol exposure, much greater following exposure to O_3 alone or to the mixture of the two

Table 2-7 (cont'd). Animal studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Shami et al. (1984)[119]	Animal/rats	36 mg/m^3 fluidized bed coal combustion fly ash Exposure duration: 4 weeks @ 7 hours/day, 5 days/week	Changes in pulmonary epithelial cells, alveolar macrophages, airway epithelial cells, and cells of the lung-associated lymph nodes 42 weeks after exposure, found thickening of the alveolar walls, clustering of particle-filled macrophages in the alveolar region, perivascular inflammation, and small granulomas in the alveolar region
Last and Pinkerton (1997) [120]	Animal/ rat	Rats exposed to 0.12 or 0.20 ppm O_3, 20, 100, or 150 ppm H_2SO_4 aerosol (0.4-0.8 μm diameter) , or some combination for up to 90 days	Exposure of rats to O_3 produced tissue and cellular changes at the bronhiole-alveolar duct junction. Combined exposure with H_2SO_4 did not affect the extent of magnitude of these changes. H_2SO_4 alone had no consistent effects.
Aranyi et al. (1983)[121]	Animal/mice	0.2 mg/m^3 O_3 0.2 mg/m^3 O_3 and 13.2 mg/m^3 SO_2 and 1.04 mg/m^3 $(NH_4)_2SO_4$ aerosol Exposure duration: 103 days @ 5 hours/day, 5 days/week Control: filtered air	Increased susceptibility to group C streptococcal aerosol infection in both exposure groups Alterations in splenic T-cell function and increased pulmonary bactericidal activity by alveolar macrophages in the mixed pollutant group
Jakab et al. (1996)[122]	Animal/mice	10 mg/m^3 carbon black aerosol and 10 ppm SO_2, low and high humidity conditions	Significant suppression of alveolar macrophage phagocytosis after high humidity exposure (when chemisorption of SO_2 onto aerosol and oxidation to SO_4^{2-} favoured)

Table 2-8. Cell studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Beck-Speier et al. (1993)[123]	Cell/ human neutrophils	PMNs were exposed to 0.01 to 1 mM concentrations of sulfite or 2 to 10 mM concentrations	Low concentrations of sulfite stimulated neutrophils to produce O_2^- through a specific signal transduction pathway.
Becker et al. (1996)[124]	Cell/human and rat alveolar macrophages	urban air particles	Increased TNF-alpha and IL-6 production
Dong et al. (1996)[125]	Cell/rat alveolar macrophages	urban air particles	Increased TNF-alpha, IL-1, IL-6, CINC, and MIP-2 gene expression
Samet et al. (1996)[126]	Cell/ Human airway epithelial cells	Exposure: ROFA, 24 hours	Increased amounts of prostaglandin H sythase products, increased PHS activity, and increased mRNA production.
Stringer et al. (1996) [127]	Cell/lung epithelium	TiO_2, Fe_2O_3, SiO_2, or concentrated ambient particles (CAP)	Cells can bind all particles tested, but do so to varying degrees through different cell receptors and different cytokine responses
Carter et al. (1997)[128]	Cell/ Normal human bronchial epithelial cells	Exposure time: 2 or 24 hours Exposure constituents: ROFA containing V, Ni, and Fe Exposure concentration: 0,5, 50, or 200 $\mu g/m^3$ ROFA	Cells produced increased IL-8, IL-6, TNF, and mRNA for these cytokines

Table 2-8 (cont'd). Cell studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Dye et al. (1997) [129]	Cell/rat tracheal epithelial cells Animal/rats	Cells were exposed to 5, 10, or 20 μg/m^3 of ROFA for 24 hours Rats were intra-tracheally instilled with ROFA (500 μg per rat)	Exposure caused cell death, detachment of cells from the collagen matrix, increased layer permeability, decreased cellular glutathione levels. DMTU inhibited the effects, D-MNA did not. Animal exposure caused pulmonary neutrophilic inflammation, which was reduced by administration of DMTU. Results suggest ROFA induces cell injury via OH- radical ROS generated via non-nitric oxide pathways, overwhelming GSH defenses
Fabiani et al. (1997)[130]	Cell/peripheral blood monocytes	Particulate extract	Reduced superoxide anion production in response to challenge Many cells died from treatment
Godleski (1997) [100]	Animal and cell/ various species	Concentrated ambient particles	Animals with pre-existing pulmonary inflammation demonstrated increased mortality Health animals demonstrated no significant effects
Goldsmith et al. (1997) [131]	Cell/hamster alveolar macrophages	Concentrated ambient particles	Increases in the production of pro-inflammatory mediators
Hitzfeld et al. (1997) [132]	Cell/polymorphonu clear leukocytes	PM_{10}	Release of reactive oxygen species
Samet et al. (1997)[133]	Cell/ Human bronchial epithelial cells (BEAS)	Exposure: ROFA	Induced increases in protein tyrosine phosphate levels. This response was mimicked by V-containing solutions, but not Fe or Ni containing solutions.

Table 2-8 (cont'd). Cell studies on the effects of particulate matter

Investigators	Type of study/species	Exposure protocol	Response
Vincent et al. (1997) [134]	Cell	Various urban dusts and $PM_{2.5}$	Different particle mixes produced different patterns of gene induction responses
Bonner et al. (1998)[135]	Cell/ rat alveolar macrophages	Rat AMs were exposed to PM_{10} samples from regions of Mexico City, or to Mt. St. Helen's volcanic ash particles as a negative control	All Mexico City PM_{10} samples induced AM secretion of a factor (probably IL-1 beta) which upregulates the PDGF alpha-receptor on rat lung myofibroblasts, which in turn regulates mesenchymal cell proliferation. Volcanic ash did not have this effect. Both vanadium, and lipopolysaccharide/endotoxin, two constituents of PM_{10}, also stimulated the release of this factor.
Ghio et al. (1998)[136]	Cell/ Respiratory epithelial cells	Exposure to 0-200 μg/ml oil fly ash for 2 and 24 hours	Concentrations of ferritin and lactoferrin increased, but concentrations of transferrin decreased. Increases suggest protection from metal-induced oxidative stress.
Goldsmith et al. (1998) [137]	Cell/hamster alveolar macrophages	Concentrated ambient particles, residual oil fly ash, and their water-soluble and particulate fractions were used in exposure protocols	ROFA and CAPs induced production of reactive oxygen species and cytokines, apparently due to metal components adsorbed to the particulate.
Kennedy et al. (1998)[138]	Cell/ Cultured BEAS-2B cells and human bronchial epithelial cell cultures	Exposed to total suspended particulates collected in Provo, Utah, and to Cu^{2+} found tin Provo extract	Both stimulated production of IL-6, IL-8, IL-8 mRNA, ICAM-1, and NF-kappaB activation
Samet et al. (1998)[139]	Cell/human bronchial epithelial cells	Exposure to As, Cr, Cu, Fe, Ni, V, and Zn at noncytotoxic concentrations	Cells exposed to As, V, and Zn demonstrated marked increase in expression of inflammatory mediator MAPK; As, V, Zn, Cr, and Cu induced IL-8.

Clinical studies on the respiratory health effects of particulate matter

Although human exposure chamber studies (also called clinical studies) are limited with regard to assessing chronic effects, rare effects, or effects from long-duration exposures, they are extremely useful in assessing acute, reversible effects from short-duration exposures in humans, and are invaluable in complementing epidemiological, animal toxicological, and in vitro data.[140] However, even among clinical studies, wide variations in methodology exist, making comparisons difficult. In general, studies vary according to the following factors:

1. Chemical composition of the particles to which subjects were exposed
2. Size of particles
3. Concentration of particles
4. Duration of exposure
5. Response measured
6. Other environmental conditions (temperature, humidity, etc.)

Since H_2SO_4 and sulphate aerosols have often been singled out as the chemical constituent of PM with the strongest relationship to health outcomes, most of the clinical research has focussed on these species or combinations of H_2SO_4 or sulphate aerosols and gaseous pollutants.

The U.S. EPA concluded that in general, acid aerosols cause few or no changes in lung function or airway responsiveness. However, exposure may cause changes in mucociliary clearance, and may potentiate the response to gaseous pollutants. Asthmatics seem to be more sensitive than healthy subjects, as evidenced by increased responsiveness to bronchoconstricting agents in adults exposed to PM, and slight changes in lung function in adolescents exposed to PM.[9,17]

The CEOHA review found that acid aerosols appear to have irritant potential that is related to their acidity. Such species have been found to cause bronchoconstriction and mild restriction of the small airways, to reduce tracheobrohchial and small airways clearance rates at high concentrations or under chronic conditions, and to alter ciliary function, but have not been found to affect pulmonary function in healthy subjects. Acid aerosols have also been found to potentiate the response of human subjects to other pollutants, such as SO_2 and O_3. Asthmatics

were also identified as a potentially sensitive group: asthmatic subjects responded with a slight reduction in FEV_1 after exposure to high concentration in some studies, and other reported responses have included enhanced nonspecific airway reactivity and bronchoconstriction, slowed mucociliary clearance, and increased upper and lower respiratory symptoms.[3]

Other constituents of PM besides sulphuric acid aerosols have been studied, although not to the same extent. The U.S. EPA reported increases in airway resistance, reductions in vital capacity in subjects with chronic respiratory disease, decreases in specific airway conductance, and decreases in flow in response to non-H_2SO_4 exposure. Again, the specific protocol followed by the investigators varied widely, but generally, high aerosol concentrations were employed, so conclusions are difficult to draw.[9,17] The studies reviewed by the CEOHA involving nonacid particle exposures in human did not produce significant effects in healthy subjects.[3]

Recent studies have also tended to produce few significant findings. Table 2-9 summarizes some of them. In all cases, very small or no significant changes have been found in response to exposure atmospheres containing H_2SO_4, H_2SO_4 in combination with other pollutant gases, diesel exhaust particles, or metal oxides at concentrations up to 1500 $\mu g/m^3$ (H_2SO_4) for durations of up to 6.5 hours. Positive findings have included changes in mucociliary clearance, increased cough, decreased lung function in asthmatic subjects, increased symptom reporting in asthmatic subjects, increased airway resistance, increased immunoglobulin production, and increases in inflammatory cell parameters.

Conclusions

Analysis of the evidence

Despite the large number of epidemiological studies that have established statistically significant associations between particulate matter exposure and various mortality and morbidity outcomes, not all researchers agree with the conclusion of a causal relationship, generally based on what are known as the Bradford Hill criteria. These attributes have been accepted as those, at least some of which should be present in order to conclude that a statistical association observed in epidemiological studies can be considered evidence of a causal relationship. Although they apply primarily to the epidemiological evidence, some of the criteria (biological plausibility,

Table 2-9. Clinical studies on the effects of particulate matter exposure

Investigators	Subjects	Exposure Protocol	Results
Horstman et al. (1982)[141]	18 exposure subjects 17 control subjects	0.5 μm H_2SO_4 108 μg/m^3 4 hours exposure Two 15 minute exercise periods	No significant change in pulmonary function
Kulle et al. (1982) [142]	12 subjects	0.3 ppm O_3, then to 100 μg/m^3 H_2SO_4 for 4 hours, with light to moderate exercise	No significant changes in pulmonary function or bronchial reactivity
Avol et al (1988) [143]	21 healthy subjects 21 asthmatic subjects	0.9 μm MMAD H_2SO_4 aerosol at concentrations of 380, 1060, and 1520 μg/m^3 for 1 hour with intermittent exercise	Healthy subjects: increased cough with increasing acid concentration Asthmatic subjects: increased irritant symptoms and decreased pulmonary function at the two highest concentrations
Avol et al. (1990) [144]	32 asthmatic subjects	0.5 μm MMAD H_2SO_4 46 ± 11 μg/m^3 and 127 ± 21 μg/m^3 40 minutes exposure 10 minutes exercise	Non-significant increases in reported symptoms and bronchoconstriction
Koenig et al. (1994) [145]	22 adolescent asthmatics	4 conditions: air 0.12 ppm O_3 and 0.3 ppm NO_2 O_3 and NO_2 and 70 μg/m^3 H_2SO_4 O_3 and NO_2 and 0.05 ppm nitric acid Two exposures to each condition 90 minutes exposure Three 15 minute exercise periods	No significant changes in pulmonary function Six (of original 28) subjects dropped out because of uncomfortable symptoms during exposure

Table 2-9 (cont'd). Clinical studies on the effects of particulate matter exposure

Investigators	Subjects	Exposure Protocol	Results
Linn et al. (1994) [146]	15 asthmatic 30 healthy	4 conditions 0.12 ppm O_3 and 100 $\mu g/m^3$ H_2SO_4 O_3 alone H_2SO_4 alone air Exposure on two consecutive days for 6.5 hours per day with six 50 minute exercise periods	H_2SO_4 alone: no changes in lung function, symptoms, or response to methacholine O_3 alone or in combination with H_2SO_4: decrease in flow and increase in bronchial reactivity, but no significant enhancement of O_3 effects with H_2SO_4 exposure
Rudell et al. (1994) [147]	8 healthy subjects	diesel exhaust 1 hour exposure	Unpleasant symptoms, but no significant changes in lung function
Bowes et al. (1995) [148]	7 healthy subjects	10 μm MMAD H_2SO_4 500 $\mu g/m^3$ pH 2.0 60 minutes exposure 20 minutes exercise control exposure: NaCl aerosol	Change in mucociliary clearance in the trachea and small airways, proportional to the estimated amount of acid inhaled orally
Frampton et al. (1995) [149]	30 healthy 30 asthmatic	100 $\mu g/m^3$ H_2SO_4 then 0.08, 0.12, or 0.18 ppm O_3 24 hours later control: NaCl 3 hours exposure each	Asthmatic subjects exposed to H_2SO_4 had an enhanced drop in FVC after exposure to 0.18 ppm O_3. An interaction effect was observed for both FVC and FEV_1 in the asthmatic group and the entire subject pool

Table 2-9 (cont'd). Clinical studies on the effects of particulate matter exposure

Investigators	Subjects	Exposure Protocol	Results
Friedrichs and Behrendt (1995)[150]	37 lung tissue samples were collected, 15 from normal lungs and 22 from cases of lung cancer	Non-fibrous mineral dust particles were examined in the tissue samples	Significant differences between the groups: number concentration of particles in the cancer group was 2 x normal, higher content of finer particles in cancer group. Composition of compounds was similar in both groups, but different from ambient air pollutant composition.
Leduc et al. (1995) [151]	14 asthmatics	9 µm MMAD H_2SO_4 500 µg/m^3 60 minutes exposure	No significant change in pulmonary function or bronchial response to methacholine challenge
Linn et al. (1995) [152]	24 asthmatics	3 conditions: 0.3 ppm NO_2, 0.2 ppm O_3, 127 µg/m^3 H_2SO_4 NO_2 and O_3 together air 90 minutes exposure Three 15 minute exercise periods	No significant differences between response to each exposure. Some subjects did respond unfavourably.
Rudell et al. (1996) [153]	12 healthy subjects	3 conditions: air diesel exhaust diesel exhaust filtered through a particle trap to reduce particle exposure by 46% 1 hour exposure Light intermittent exercise	Airway resistance and specific airway resistance increased following exposure to diesel exhaust. The particle trap did not attenuate these changes
Churg and Brauer (1997)[154]	Autopsy lung tissue from the bodies of 10 nonsmokers	Analytical electron microscopy of the upper lobe apical segment parenchyma	96% of particles had an AD less than 2.5 µm

Table 2-9 (cont'd). Clinical studies on the effects of particulate matter exposure

Investigators	Subjects	Exposure Protocol	Results
Kuschner et al. (1997) [155]	6 healthy volunteers	MgO particles	No change in pulmonary function or inflammatory markers
Linn et al. (1997) [156]	41 subjects (healthy, allergic, and asthmatics) thought to be sensitive to acid summer haze	0.1 ppm O_3, 0.1 ppm SO_2, 100 ± 40 $\mu g/m^3$ H_2SO_4 4 hours exposure intermittent exercise	No significant changes in spirometry, symptoms, or overall discomfort. Allergic and asthmatic subjects showed a positive association with reported symptoms and estimated acid dose, but healthy subjects showed a negative association
Ghio et al. (1998)[157]	22 volunteers	Instilled with 20 ml saline in right middle lobe bronchus Instilled with 20 ml of an iron-containing particle suspended in saline in lingular bronchus Lavage 1, 2, or 4 days after exposure, and measure of lactoferrin and L-ferritin, and transferrin	Ferritin and lactoferrin concentrations increased, transferrin concentrations diminished, probably in order to decrease the oxidative stress of metal exposure.
Lay et al. (1998) [158]	30 healthy volunteers	Instilled with 2.6 μm diameter iron oxide particles; BAL used to sample retention of particles in the alveolar macrophage compartment at times from 1 to 91 days post-instillation.	Increased neutrophils and AM in BAL fluid 24 hours post-instillation. Particle clearance had a biphasic pattern, with rapid clearance of AMs with high particle burdens (half-time 0.5 days) and a long term clearance of AMs with lower particle burdens (half time 110 days)

coherence, and experimentation) include the entire body of evidence, including animal, cell, and clinical studies.[2]

These criteria are:

1. Strength of association. The strength of the association (as measured by the risk ratio) or the size of the regression coefficient is an important factor in determining causation. If the association is weak, bias or confounding influences can more easily account for the relationship, and conversely, if the association is strong, there is little question of statistical accuracy, and a case can be made for a cause-effect relationship.[2,159,160] A risk ratio of less than 1.5 to 2.0 is generally considered weak.[161]

In the case of particulate matter exposure, the 1952 London air pollution episode, during which the mortality rate tripled, is a good example of a strong association. The cause-effect nature of this relationship is generally well established.[2] However, the cause-effect nature of the associations which have been observed in more recent studies of much lower exposure, where the risk ratios are only slightly above one, are questionable. Furthermore, reported R-squared values, a measure of the degree to which the variability in the data is explained by the statistical model, indicate that little of the variability is actually explained by particulate matter exposure even when statistically significant associations are observed.[160]

The low risk ratios and R-squared values reported do not rule out the possibility that incomplete adjustment for confounding variables (such as weather, co-pollutants, seasonal changes, etc.) is the true underlying cause of the association, rather than particulate matter exposure.[160] However, since exposure is not high, such small risk ratios may be expected. What this criterion indicates for the evaluation of epidemiological studies on the health effects of particulate matter exposure is that other criteria must be met before causality can be assigned.

2. Consistency of association. The association must be demonstrated in different studies using different populations in different places at different times, by different researchers. This has generally been the case for particulate matter, as studies from Europe and North America have been broadly consistent in findings.[16,17] However, not all studies have found positive results, though this may be related only to strength of association. For example, a recent study done in Toronto found that particulate matter could not be considered an independent contributing risk factor for cardiac or respiratory morbidity.[162] Furthermore, both measures of

exposure and measures of outcome have varied considerably between studies, so consistency is difficult to determine.

3. Temporality of association. The association must always follow the same order: exposure first, then response. This appears to be the case, especially since many mortality and morbidity studies have found associations between a 1 to 3 day lagged particulate exposure and a particular outcome.[2] However, there is still considerable variation among many studies with respect to the lag time between exposure and mortality or morbidity outcome, and this weakens the argument for temporality, as well as the argument for consistency.

4. Dose-response relationship. A higher dose or exposure should produce a greater effect, and a lower dose or exposure a lower effect. Such a relationship is difficult to determine because dose is difficult or impossible to determine for large samples. However, comparing the studies of air pollution episodes in London in the 1950's and 1960's and New York in the 1960's,[2] when exposure was higher than today, to more recent work, does suggest that a dose-response relationship could be inferred. Furthermore, long-term exposure studies such as the Six-City study and the American Cancer Society study suggest that a linear exposure-response relationship exists. Nevertheless, such conclusions are limited by evidence which indicates that personal exposure and outdoor central site measurements are not well correlated.[163]

5. Biological plausibility. It would be helpful if there was a biological mechanism to account for the observed effects. The value of the animal and cell toxicology research lies in the fact that it can shed light on the underlying mechanism that may explain the associations observed in the epidemiological literature. To that end, simply showing any effect is not helpful, and many studies that do just that must be viewed cautiously, since the concentration, duration, and physical and chemical composition of the exposure is generally much different than ambient conditions, and the target organism is of course very different as well. However, studies which have demonstrated inflammation, increased airway resistance, increased airway reactivity, decreased mucociliary clearance, decreased pulmonary function, and impaired host defence, in response to exposure to reasonable concentrations of specific pollutants known to be part of the chemical composition of particulate matter, are indeed valuable. They suggest possible mechanisms (such as chronic inflammation, decreased clearance, and altered host defences) whereby increases in mortality, exacerbation of respiratory illness, and the development of

respiratory symptoms and illnesses such as chronic cough, bronchitis and COPD can plausibly be linked to acute and chronic exposure to particulate air pollution. What is still required is supporting evidence from controlled studies in humans.

6. Specificity of association. The associations are generally of a respiratory nature, although associations with measures of cardiovascular mortality and morbidity have also been observed.[2,3,9,17] Satisfying this criterion faces the same problem as the consistency and temporality criteria in that studies have varied widely in their measures of both exposure and outcome, both with respect to the actual measure and the time between exposure and outcome.

7. Coherence. The entire body of research on the subject should be in agreement with itself. The clinical data is certainly lacking in this respect. In fact, the clinical studies suggest that particulate matter exposure has little or no effect on the respiratory system in humans. However, data from epidemiological studies suggest otherwise, and data from animal and cell studies are beginning to support the epidemiological evidence. The fact that clinical studies to date have rarely produced positive results may be because subjects are not exposed to the same ambient pollutant mix experienced in the urban environment, thereby missing a critical part of the exposure condition. This gap in the research knowledge must be bridged in order to form solid conclusions about the health effects of particulate air pollution. [164, 165]

8. Experimentation. Controlled studies in which animals and humans are removed from and exposed to particulate pollution should have the effect of removing or producing the hypothesized reaction. Again, clinical studies are not supportive of the epidemiological data, and further research is therefore required.[2,3,9,17]

Relevance to the present research

The weakness of the epidemiological literature, as assessed by the Bradford Hill criteria, can be summarized as follows: the exact relationship between exposure and outcome has not been well defined. Neither exposure, nor outcome, nor the time lag between exposure and outcome, have been measured consistently. Since these basic factors have been ill-defined, epidemiological criteria alone are not sufficient to support the argument of causality. Animal and human studies which expose the subjects to particulate matter of the same physical and chemical

nature as ambient air are required in order to identify biological mechanisms and provide coherence to the scientific literature.

Animal and cell toxicology studies on the effects of PME are beginning to offer real support to the epidemiological literature. What is still required is that these animal models of effect be confirmed by human exposure studies. Of course, chronic high concentration exposures of the kind carried out in animals is unacceptable, but the true strength of the recent animal research is that it has become more relevant to the supportive role which is required of it. By designing experiments that use high but reasonable levels of exposure concentration to PM that reflects the complex chemical composition of the ambient environment, new insights into possible mechanisms that would explain the epidemiological literature are emerging. Human exposure studies are required which follow that lead by exposing subjects to concentrations of PM that accurately reflect the composition in the ambient environment, to help prove or disprove the existence of a causal relationship between PME and the human health outcomes seen in the epidemiological literature.

Clinical studies are the real missing link in the literature on the health effects of PME. There are no definitive studies that can offer convincing evidence one way or the other for an effect of PME on any measured endpoint. This shortcoming may be due to the physical and chemical nature of the particulate matter to which subjects are exposed. Since no single chemical constituent has been identified as the likely causative agent, it is probable that its complex composition gives PM a unique toxicity. Such complex composition must therefore be reflected in the controlled human exposure studies of health and health-compromised individuals if definitive research is to be accomplished. Since the present research addresses these issues thoroughly, it is therefore necessary, relevant, and unique to the scientific database.

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Chapter Three: Characterization of a human exposure facility for the study of the effects of particulate matter exposure on respiratory and cardiovascular health

Introduction

As noted in Chapter Two, there is a lack of clinical data supporting the epidemiological evidence on the health effects of particulate matter exposure. The evidence that does exist is based on the artificial exposure constituents that are generally employed, even single chemicals (especially H_2SO_4) or simple combinations of chemicals, which are not representative of the real-world situation.[1,2,3] To aid in filling this knowledge gap, a team of researchers at the Harvard School of Public Health have developed an ambient particle concentrator utilizing the technique of virtual impaction, which allows the concentration of ambient particles within a certain range of aerodynamic diameter without changing the size distribution or chemical composition of the ambient particulate mix.[4, 5, 6]

A human exposure facility (HEF) was developed at the University of Toronto using the Harvard ambient particle concentrator (HAPC). The purpose of the present study was to characterize that facility, by running preliminary exposure trials, with the goal of testing the following hypotheses:

1. That independent measures of $PM_{2.5}$ concentration (DustTrak aerosol monitor and gravimetric analysis of collected filter samples) are in good agreement, and therefore can provide complementary data on exposure.
2. That stable target $PM_{2.5}$ concentrations can be achieved in the exposure chamber (EC) using ambient air as the particle source, by adjustment of the HEF settings.
3. That EC temperature and relative humidity remain within a comfortable range, and that EC pollutant gas concentrations do not differ from ambient levels, throughout each exposure trial.
4. That exposure to controlled concentrations of $PM_{2.5}$ has a concentration- and time-dependent effect of pulmonary function.

In this chapter, the first three hypotheses were examined.

Materials and Methods

Human exposure facility

The facility consisted of a source of ambient air, a source of filtered dilution air, a particle size-selective device to remove particles larger than 2.5 micrometers in aerodynamic diameter, a two-stage virtual impaction concentrator, and a chamber in which to expose human subjects.

Pumps

A series of pumps drew air from ambient and filtered air sources through the two stages of the Harvard ambient particle concentrator and then through the HEF chamber. One pump drew air through the major flow of the first stage of the HAPC at a flow rate of approximately 880 L/min. Another drew air through the major flow of the second stage of the HAPC at a flow rate of approximately 220 L/min (Gast Model 1023-101Q-G608X, Benton Harbor MI). A third pump drew air through the chamber at a flow rate of approximately 45 L/min. A sampling pump drew an additional 15 L/min through the chamber air delivery pipe.

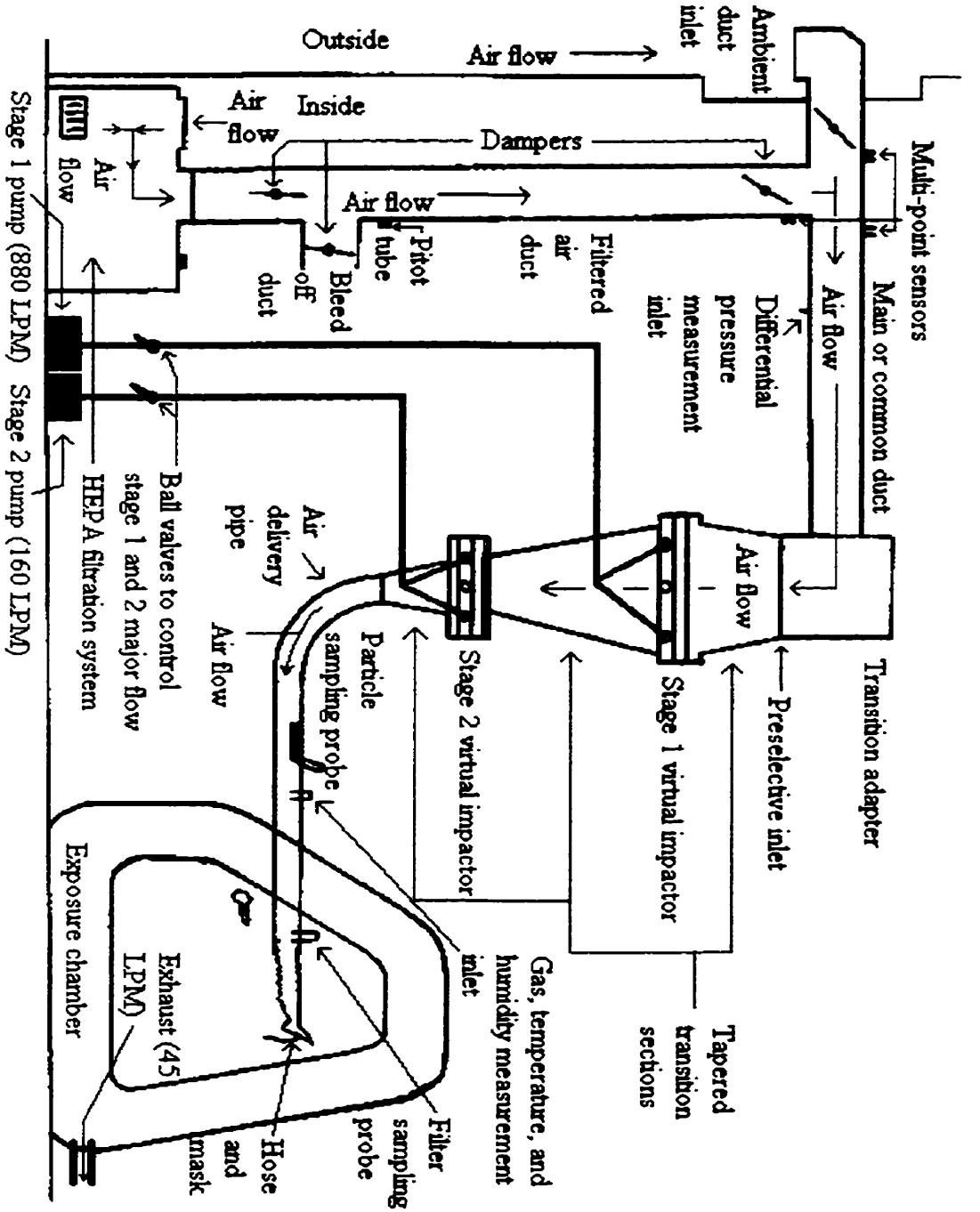
Ambient and filtered air inlets

The pumps drew air from these two sources through the HAPC and into the EC. The source of ambient air was a duct (20 x 20 cm) facing downwards, 11 metres above the ground, outside of the laboratory at 223 College Street (Fig. 3-1). The ambient air was drawn upwards and immediately redirected at a 90° angle, through a galvanized steel duct. Such redirection is known to cause loss of large particles due to impaction.

The source of particle-free air was laboratory room air filtered through an Amaircare HEPA Air Filtration System (Model 4000V, Americair Corp., Mississauga ON), a three stage air filter. Air entered the filtration system through ducts on the top and sides of the unit. The first filtration stage consisted of a non-woven polyester filter (0.48 cm thick) impregnated with activated carbon, that removed large particles and volatile organic compounds (VOCs). The second stage consisted of a HEPA 3000 Grade borosilicate filter rated to remove 99.97% of the particles larger than 0.3 μm. The third stage consisted of another non-woven polyester filter (1.27 cm thick) impregnated with activated carbon. After passing through the filter stages, the

air was exhausted through the top of the unit, into a branch duct that joined the ambient air duct to form a common or main duct connecting the two air sources to the HAPC (Fig. 3-1).

Figure 3-1. Schematic diagram of the human exposure facility



Preselective duct

The main duct delivered air from ambient and filtered sources to a stainless steel transition adapter, which redirected the air 90° downwards (Fig. 3-1). This redirection was necessary to allow the HAPC to be placed in a vertical rather than horizontal position, to allow for periodic maintenance. The redirected air then passed through a preselective inlet, a Sierra High Volume Cascade Impactor (Sierra-Misco Inc.). The preselective inlet impactor consisted of two anodized aluminum alloy plates with 10 slots, each of dimensions 11.8 cm x 1.5 mm. A glass-fibre collection paper of dimensions 14.8 cm x 14.2 cm, also containing slots, was placed between the two plates. The slots of the collection paper were aligned with the downstream plate, and these were staggered with respect to the upstream plate. Thus, particles larger than a given aerodynamic diameter impacted on the collection paper, while the smaller particles followed the airstream through the slots of the downstream plate and continued with the gases. The width of the impactor slots and the flow of the air passing through them determined the cut-point of the impactor. At 40 CFM (1163 L/min), this impactor had a 50% cutpoint at aerodynamic diameter 2.5 μm, so that 50% of the particles of aerodynamic diameter 2.5 μm were impacted, and 50% continued with the airstream.

Concentrator

Downstream of the size-selective inlet, the air passed through a tapered transition section, and then through the first virtual impactor (Fig. 3-1, 3-2). The virtual impactor works by drawing air through an acceleration nozzle by pumps operating at two different flow rates. One pump draws the major flow of air through the acceleration nozzle, and then at low velocity along a deflected path. Another pump draws air at a much lower flow rate but at high velocity through a collection slit, along a straight streamline. This is known as the minor flow. The extremely narrow acceleration nozzle causes the air passing through it at a constant flow rate to accelerate in order to maintain that flow rate. The acceleration provides momentum to the particles in the air. Once through the acceleration nozzle, particles in the air which are larger than a certain size continue along a relatively straight path into the collection probe because of their greater momentum, following the minor flow, while most of the air, and most of the smaller particles, follow the deflected streamlines of the major flow. As a result, the concentration of particles in the minor flow increases by a factor of Q_T/q_m, where Q_T is the total flow entering the acceleration nozzle and q_m is the minor flow.

The stage 1 virtual impactor of the HAPC consisted of an acceleration nozzle of dimensions 0.3429 mm x 304.8 mm, and a collection slit of dimensions 0.508 mm x 304.8 mm. Both nozzle and slit contained a 25.4 mm closed space in the middle of the slit. The collection slit is slightly wider than the acceleration nozzle, in order to minimize particle losses due to impaction on the tip of the collection slit. The theoretical flow rates through stage 1 was 1100 L/min, 880 L/min through the major flow, and 220 L/min through the minor flow.

At this slit size and flow rate, most of the particles of aerodynamic diameter 0.15 μm or less followed the major flow airstream. However, most of the particles larger than this had sufficient momentum to continue in a straight path through the 'collection nozzle' along the minor flow airstream. This resulted in a depletion of particles in the range 2.5 to 0.15 μm aerodynamic diameter in the major flow, and an accumulation in the minor flow. Thus the mass concentration of particles in the minor flow was increased. The actual concentrating power of the stage 1 virtual impactor was determined by the ratio of total to minor flow, which was 1100 L/min to 220 L/min, for a theoretical concentrating power of approximately 5.0.

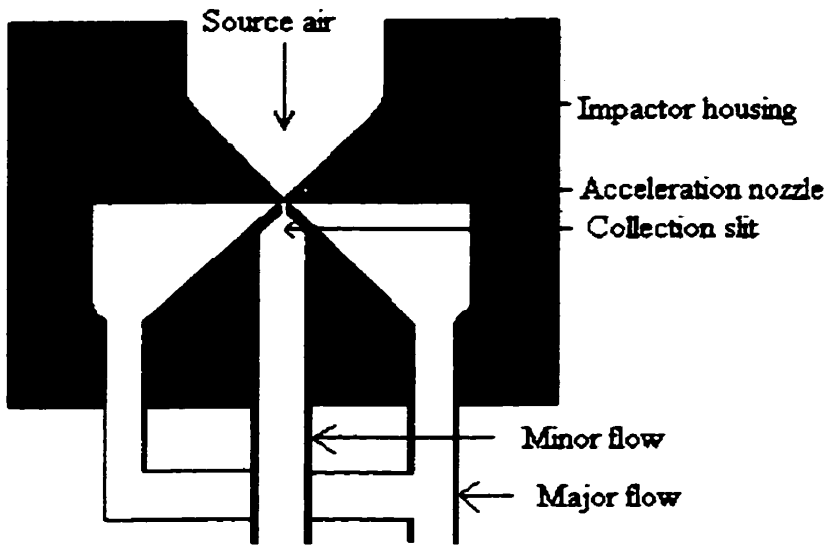
Air from the major flow was released back into the ambient air. Air from the minor flow was drawn through a second transition section, and into the second virtual impactor (Fig. 3-1, 3-2). This consisted of an acceleration nozzle of dimensions 0.3429 mm x 55.88 mm, and a collection slit of dimensions 0.508 mm x 55.88 mm. The total to minor flow ratio of the second stage was 220 L/min to 60 L/min, and therefore the theoretical concentrating factor for particles in the size range 0.15 to 2.5 μm through the second stage of the HAPC, was approximately 3.7. The theoretical total concentrating factor for the two-stage concentrator was 18.5 times ambient levels (the product of the individual concentrating factors), minus within-stage and between-stage losses of approximately 15% which were known to occur, for a total concentrating ability of approximately 13.4.[3]

Chamber

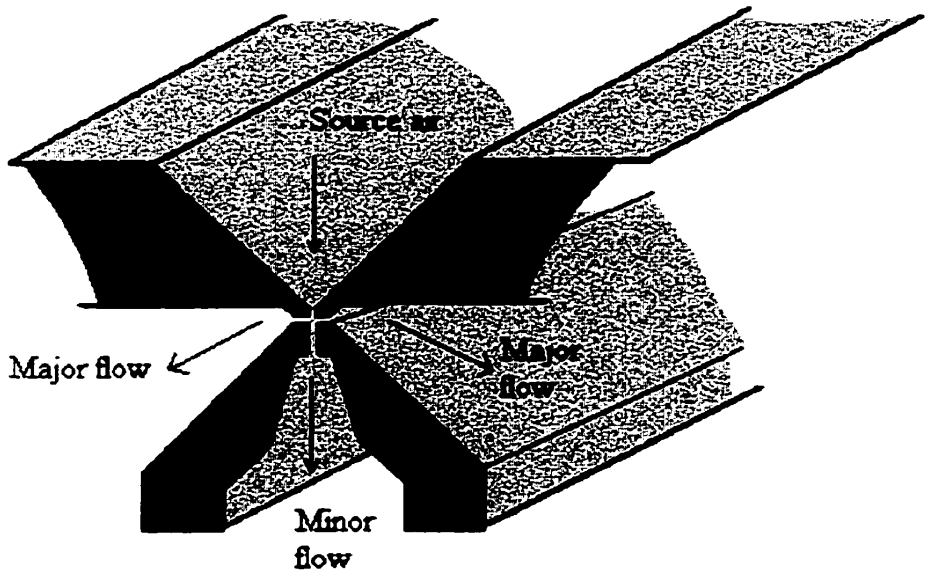
The minor flow of the second stage virtual impactor, containing the concentrated particles, was drawn by a pump operating downstream of the exposure chamber (Airco 310 Plethysmograph Cabinet, Ohio Medical Products, Houston TX), and a pump sampling particles inside the EC, at a combined flow rate of approximately 60 L/min.

Figure 3-2. Schematic diagram of the virtual impactor

Part A. Overview



Part B. Impactor detail



The particle-concentrated air was drawn from the second stage virtual impactor through a third transition section, to a stainless steel delivery pipe bent gradually to divert the flow 90° and into the EC (Fig. 3-1). The air delivery pipe was connected to a flexible hose attached to a standard oxygen mask, through which the subject breathed the particle-concentrated air. Finally, the air was exhausted through a pipe at the base of the chamber.

Air monitoring

Multi-point Sensors (Diamond Flow Sensor, Nailor Industries, Toronto), were used to estimate air flow in the ducts (Fig. 3-1). The Multi-point Sensor measures the pressure difference between inlets facing the air flow (velocity and static pressures) and those perpendicular to the air flow (static pressure). Sensors were placed in the ambient air duct, in the filtered air duct, and in the common air duct supplying the HAPC. These sensors have an accuracy of ±5% and a minimum differential pressure detection capability of 0.012 in.w.g., which translates into a duct air flow of approximately 1550 L/min. The differential pressure was calculated by an electronic micromanometer (Air Data Multimeter, Model ADM-850, Shortridge Instrument Inc., Scottsdale AZ). To minimize instrument error, five readings were taken at each sensor, and averaged, every 15 minutes during each trial. The average differential pressure was then converted to an air flow value by the standard formula:[7]

$$Q = 4005(\sqrt{\Delta P})A$$

where

Q = flow in cubic feet per minute

ΔP = velocity pressure in inches of water gauge

A = cross-sectional area of the duct in square feet

For a circular duct with diameters of 6 inches, and adding a unit conversion to yield flow in litres per minute, the formula became:

$$Q = 14170 \times (\sqrt{\Delta P})$$

where

Q = flow in litres per minute

ΔP = velocity pressure in in.w.g.

A Pitot tube inserted in the duct near the HEPA filtration system exhaust was used to measure air flow through the filtered air duct as well (Fig. 3-1). The side holes of the Pitot tube experience static pressure, and the nozzle experiences static and velocity pressure. The differential pressure therefore yields velocity pressure. The Pitot tube has a minimum air velocity detection capability of 600 foot per minute, which translates to a flow through the filtration system duct of approximately 875 L/min. The differential pressure was calculated by an electronic micromanometer (Air Data Multimeter, Model ADM-850, Shortridge Instrument Inc., Scottsdale AZ). Five readings were taken, and averaged, every 15 minutes during each trial. The average velocity pressure, in inches of water gauge, was converted to flow rate in litres per minute by application of the standard equation, given a circular duct diameter of 3 inches, which yielded the following formula:[7]

$$Q=5829 \times (\sqrt{\Delta P}) = \text{flow rate (L/min)}$$

The differential pressure between the laboratory room atmosphere and the pressure in the common or main duct was monitored near the transition adapter (Fig. 3-1) to assure that the HAPC was not being overpressurized. A positive pressure reading would indicate overpressurization, that is, that filtered air was being pushed into the HAPC (by the HEPA filtration system), rather than the air being pulled through the HAPC by the pumps. This would mean that the HAPC would not be operating to design specifications. The differential pressure was measured by an electronic micromanometer (Air Data Multimeter, Model ADM-850, Shortridge Instrument Inc., Scottsdale AZ). To minimize instrument error, five readings were taken, and averaged, every 15 minutes during each trial.

Pressure in the major and minor flows of both stage 1 and stage 2 of the HAPC was measured by Magnehelic Pressure Gages (Dwyer Instrument Inc., Michigan City IN). Stage 1 and stage 2 major flows could be adjusted with ball valves, which would change the measured pressure (Fig. 3-1). The specifications for the HAPC were such that stage 1 and 2 major pressures of 120 in.w.g., stage 1 minor pressure of 2.5 in.w.g., and stage 2 minor pressure of 5 in.w.g., would yield a stage 1 major flow of 880 L/min, a stage 1 minor flow of 280 L/min, a stage 2 major flow of 220 L/min, and a stage 2 minor flow of 60 L/min. Pressure readings for the stage 1 major flow, stage 1 minor flow, stage 2 major flow, and stage 2 minor flow were

recorded every 15 minutes during each trial.

Particle concentration monitoring and control

To control the particle concentration of the air delivered to the EC, various adjustments were made. Coarse control over EC $PM_{2.5}$ concentration was achieved by one or a combination of the following methods (see also Fig. 3-1):

1. The ambient and filtered air ducts contained dampers which could be electrically controlled to adjust the flow from each source, and thus the $PM_{2.5}$ concentration of the air upstream of the HAPC.
2. Stage 1 and 2 major flow channels had ball valves in place which could be adjusted to change the major flows, and therefore the ratios of total to minor flow, and therefore the concentration factor of the HAPC.
3. The filtered air duct contained a damper that could be adjusted by hand to control the flow of air through the duct, and thus the degree of dilution of the air upstream of the HAPC..
4. The filtered air duct contained a bleed-off duct as well, which could also be adjusted to control the flow of filtered air reaching the main duct, and thus the degree of dilution of the air upstream of the HAPC as well.

These adjustments were generally made prior to the exposure trial. During the exposure, fine control over the EC $PM_{2.5}$ concentration was achieved by the adjustment of the speed of the fan drawing air into the filtration system and out into the filtered air duct. The flow rate that could be generated by the HEPA filtration system blower fan ranged from approximately 2100 to 8500 litres per minute, according to the manufacturer's rating, but because of the additional static pressure created by the connecting ductwork, the actual flow range was approximately $1/10^{th}$ of the rated flow.

Particle concentrations were measured by two methods: direct reading instruments and gravimetric filter analysis. The direct reading instruments were DustTrak aerosol monitors (Model 8520, TSI Inc., St. Paul MN). These monitors use light scattering technology to determine mass concentration. A pump draws sample air into a sensing chamber of fixed volume, where the particle stream is illuminated with a laser. The particles will scatter the unidirectional laser light in all directions. A collecting lens positioned at a 90° angle to both the air stream and the laser beam collects some of the scattered light and focuses it onto a

photodector, which converts the light into a voltage. The voltage is proportional to the amount of light scattered, which is proportional to the mass concentration of the particles, so a conversion is made to give a mass concentration readout on the LCD display of the device.

The amount of light scatter is dependent on particle size, especially for particles less than 0.25 μm, and the smallest detectable size is approximately 0.1 μm. Particles in the range 0.25 to 0.1 μm are more likely to give an underestimate of the actual mass concentration. In addition, the amount of light scatter is also dependent on the composition and density of the particles, since different particles have different indices of refraction and different light absorbing characteristics. The monitor is calibrated against Arizona Test Dust, which consists of aerosols of different size, shape, and composition, in order to average the effects of size and composition on the measured signal. However, Arizona Test Dust size and composition differs from Toronto ambient air, and therefore the measured DustTrak values must be calibrated against locally collected filter sample measures of particle concentration.

A sampling probe designed to provide isokinetic sampling was placed in the delivery pipe just upstream of the EC, and connected via Tygon tubing to a DustTrak aerosol monitor, to monitor the particle concentration of the air entering the EC. Outside $PM_{2.5}$ concentration was monitored by a second DustTrak aerosol monitor, fitted with an impaction plate and an impactor with a 2.5 μm cutpoint. Instantaneous and time-weighted average values were recorded every 15 minutes during each trial. Each monitor also logged one minute average concentrations for each minute of sampling, as well as an overall time-weighted average concentration.

Air particle sampling and gravimetric analysis of collected samples was also carried out. A sampling probe was placed in the delivery pipe just inside the EC and connected to a 47 mm 'Zeflour' PTFE (Teflon) 2 μm pore-size filter (Gelman Sciences, Ann Arbor MI) enclosed in a Teflon-coated aluminum filter holder (URG, Carrboro NC) upstream from a Gast pump (Model #0523-1010-G582DX, Gast Manufacturing Corp., Benton Harbor MN), operated at either 10 or 15 L/min (laboratory temperature and standard pressure). The flow was controlled by a mass flow controller (Type 1159B, MKS Instruments, Andover MA), and monitored with a power supply readout device (Model 246B, MKS Instruments, Andover MA). The mass flow controller monitors and maintains a specific mass flow rate (±1%), and the readout device gives a value for volumetric flow rate, referenced to standard temperature. These values were corrected for the

actual EC temperature recorded.

Ambient air sampling for particles was accomplished using the same type of filter and holder as that used inside the chamber. The sampler (upstream of the filter) was a glass elutriator/impactor with a 2.5 μm aerodynamic diameter particle cutpoint, positioned outside the north window of the laboratory, and connected to a Gast pump (Model DOA-P104-AA) operating at a flow rate of 20 L/min. Flow was controlled by a mass flow controller (Model 1259C, MKS Instruments, Andover MA) and monitored with a power supply readout device (Model 246, MKS Instruments, Andover MA). The recorded flow was corrected for temperature.

In both cases, filters were preweighed, and then weighed after sampling, with a calibrated microbalance (Model AD-6, Perkin Elmer, Norwalk CT) after conditioning at 30% relative humidity and 22°C for 48 hours. The sample mass, sampling flow rate, and sampling time were used to calculate $PM_{2.5}$ concentration. NIOSH recommends that a minimum sample weight of 100 μg be collected to ensure the accuracy of the filter method.[8]

The quality of the collected samples was assured by the use of blanks and conditioning procedures. Four holder blanks (filters placed in holders but not attached to a sampler) and two bench blanks (filters placed in petri dishes) were weighed at the same time as the sample filters. Sample weight was determined by subtracting the pre-sampling filter weight from the post-sampling filter weight, and then subtracting the average difference of the post- minus pre-sampling holder blank weights from that value. Holder blank pre- and post-trial weighing compensates for contamination associated with the collection process outside of sampling itself. Bench blank pre- and post-trial weighing compensates for contamination outside of sampling and placing the filters in holders, i.e. it is a quality control measure to assure that the holder blanks are not contaminated. In addition, conditioning reduces the variability contributed by changes in the moisture content of the filter and sample.

Gaseous concentration monitoring

Six gases, namely carbon dioxide (CO_2), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), nitrogen monoxide (NO, also known as nitric oxide), ozone (O_3), and carbon monoxide (CO), were measured in the air just upstream of the exposure chamber, and in the ambient air. The

same port was used to measure all the gases in the EC air delivery pipe. Ambient CO_2 was sampled outside the east window of the laboratory, and all other ambient gases were sampled outside the north window, approximately 1.5 metres below the ambient air inlet.

Carbon dioxide concentration in the EC air delivery pipe and in the ambient air was measured by an infrared CO_2 gas analyzer (Model PM3, ADC Ltd., Hoddesdon, England). The CO_2 gas analyzer is based on the infrared-absorbing property of CO_2. A beam of infrared radiation is reflected down the cell containing the sample gas, and a detector at the other end of the cell measures the IR radiation that is not absorbed by the sample gas. The IR signal that is received after passing through the sample gas is compared to a reference cell signal, and used to determine the concentration of CO_2 in the sample gas. The analyzer has a range of 0 to 5000 ppm with a precision of ±2%. Measurements of both ambient and EC air delivery pipe CO_2 concentration were recorded every 15 minutes during each trial.

Concentrations of SO_2, NO_x (NO_2 and NO), O_3, and CO were also measured continuously for two hours on the day of each trial. During each trial, one gas was always sampled from the EC air delivery pipe, the other four from the ambient air. The gas that was sampled from the EC air delivery pipe was alternated every 15 minutes, following the same order: SO_2, NO_x, O_3, and CO.

To measure SO_2, a fluorescent SO_2 analyzer (Model 8850, Monitor Labs Inc., San Diego CA) was used. The fluorescent SO_2 analyzer measures the SO_2 concentration in a sample of air by allowing UV light to pass through the sample, which causes the SO_2 molecules in the air sample to become excited and fluoresce. A photodetector measures the fluorescent output, which is proportional to the concentration of SO_2 in the sample. The analyzer has two ranges of detection, one from 0 to 250 ppb, the other 1 to 10 ppm. Accuracy is ±3%, and precision ±0.0005 ppm. The lower detectable limit is 0.001 ppm.

To measure NO_2 and NO, a gas-phase chemiluminescence detection nitrogen oxides analyzer (Model 8840, Monitor Labs Inc., San Diego CA) was used. This device measures the chemiluminescence of an activated NO_2 species produced by the chemical reaction between O_3 and NO in an evacuated chamber. Sample air containing NO is allowed to mix with dried air containing O_3. The NO and O_3 react to produce O_2 and an activated species of NO_2, denoted NO_2^*. When the activated species reverts to a lower energy state, it emits a specific radiation

signature whose intensity is measured by a photomultiplier tube and converted to an NO concentration. NO_2 is measured in a separate sample stream, in which the NO_2 in the sample gas is first reduced to NO via a metal catalyst (molybdenum), and the NO concentration is then measured as described above. This gives the sum of the concentrations of NO and NO_2. The concentration of NO_2 is calculated by subtracting the NO signal from the NO + NO_2 signal. The NO_x analyzer has a range of 0 to 10 ppm, with a precision of ±0.8 ppb at a sample concentration of 100 ppb, and ± 1.0 ppb at 400 ppb. The minimum detectable concentration is 1.3 ppb.

To measure O_3, an ozone monitor (Model 1008-RS, Dasibi Environmental Corp.) was used. UV light of a frequency that is absorbed by O_3 is passed through an air sample of specific path length. The degree of attenuation of the UV light, as measured by a photodiode detector, is a function of the path length, the wavelength of the light, and the concentration of O_3 in the sample. The actual O_3 concentration is measured by comparison of the UV light attenuation through the sample gas and through the sample gas scrubbed of O_3 by a catalytic converter and selective gas filter. The analyzer has a range of 0 to 1000 ppb, with a lower detectable limit of 2 ppb and a precision of 1 to 2 ppb.

To measure CO, a gas filter correlation carbon monoxide spectroscopy analyzer (Model 48, Thermo Electron Instruments) was used, which is based on the IR absorption characteristics of CO. This analyzer allows a beam of IR radiation to pass through a cell of sample gas and then fall on an IR detector which measures the intensity of the IR radiation. Prior to passing through the sample cell, the IR radiation is alternately passed through a CO or N_2 filter. The CO filter produces a reference IR beam that cannot be further attenuated by CO in the sample gas. The N_2 filter is transparent to IR radiation, and therefore the radiation passing though the cell can be absorbed by CO in the sample. Comparison of the intensity of the IR radiation reaching the detector after passing through one filter or the other gives a measure of the CO concentration in the sample gas. The analyzer has a range of 0 to 1000 ppm, with a lower detectable limit of 0.10 ppm, and a precision of ±0.10 ppm.

Temperature and relative humidity monitoring and control

Temperature and relative humidity were measured in the air delivery pipe just upstream of the EC by a thermo-hygrometer (Hygrotest Testo 6400, Baker Instruments, Concord ON). Temperature was also measured inside the EC with an Ashcroft bimetal thermometer with a

range of 0 to 50° Celsius. Relative humidity was measured inside the EC with a Vaisala humidity transmitter (Model HMW-20-UB, Helsinki). The instrument's sensor transmits a current output in response to the humidity in the air. The output current, read by a Micronata digital multimeter (Model 22-166A, Intertan Canada Ltd., Barrie), has a range of 4 to 20 mAmp, and was converted to a relative humidity value by the formula:

[Current (mAmp) - 4] x 16 = Relative humidity (%)

Temperature in the EC could be controlled inside the chamber by adjusting the speed of a fan blowing air over a water-cooled copper coil. Adjustments to the temperature in the EC could also be made by adjusting the temperature of the water flowing through the coil. The relative humidity inside the exposure chamber could not be controlled, except to the extent to which it was affected by the temperature.

Temperature was measured outside the laboratory, near the ambient duct of the human exposure facility, by a mercury thermometer. Outside temperature, pressure, wind speed and direction, dew point, relative humidity, and visibility, were also recorded for the city of Toronto before, during, and after each trial, from data provided by the Canadian Meteorological Centre of Environment Canada.

Statistics

The following analyses were performed to test the stated hypotheses:

1. To test that independent measures of $PM_{2.5}$ concentration were in good agreement,

   a. Measured DustTrak and filter $PM_{2.5}$ concentration values were entered into a linear regression equation without intercept and excluding the filtered air trials. The value of the slope of the regression line was then applied to the measured DustTrak values to obtain a corrected value. This was done because previous tests indicated that DustTrak values overestimated the $PM_{2.5}$ concentration as measured by filter samples, and therefore needed to be calibrated to the filter data. The corrected DustTrak values were used in all future calculations.

   b. A Pearson correlation coefficient was calculated to determine the degree of correlation between the DustTrak and filter $PM_{2.5}$ concentration values.

c. A t-test was calculated for the mean difference between DustTrak and filter values of $PM_{2.5}$ concentration.

d. These procedures were carried out for both EC and ambient $PM_{2.5}$ measurements.

2. To test that target $PM_{2.5}$ concentrations could be achieved in the EC with good stability using ambient air as the particle source by adjusting the HEF settings, the analyses below were conducted.

   a. To test that target concentrations were achieved, the DustTrak and filter $PM_{2.5}$ measurements were each compared to the corresponding target concentration, by the calculation of Pearson correlation coefficients and t-tests of the mean difference between the measured value and the target value.

   b. To test the stability of the $PM_{2.5}$ concentration during each trial, the coefficient of variation (CoV) of the mean EC $PM_{2.5}$ concentration was noted for each trial, and compared with the CoV of the mean ambient $PM_{2.5}$ concentration. In addition, a graphical examination of the percentage change from the overall mean concentration during each trial was conducted for both the EC and ambient DustTrak data.

   c. To test the influence of the source concentration, a Pearson correlation coefficient was calculated for the degree of correlation between the EC and ambient $PM_{2.5}$ concentrations, for both DustTrak and filter data. A lack of correlation would indicate a lack of influence of the ambient $PM_{2.5}$ concentration on the EC $PM_{2.5}$ concentration.

   d. To test the effect of the ambient $PM_{2.5}$ concentration and the adjustments made to the HEF settings on the EC $PM_{2.5}$ concentration, a regression model was developed. The $PM_{2.5}$ concentration of the air entering the concentrator was estimated by the product of the ambient $PM_{2.5}$ concentration and the proportion of the total flow contributed from the ambient duct. The overall concentration factor was estimated by the quotient of the total flow and the stage 2 minor flow. It was theorized that the mean EC $PM_{2.5}$ concentration would obey the following function:

      mean EC $PM_{2.5}$ = mean ambient $PM_{2.5}$ x (mean ambient duct flow rate / sum of mean EC air flow rate and mean filter sampling pump flow rate).

Due to the interrelatedness of these variables, a new variable, equal to the right hand side of the equation above, was created, and analyzed for linear regression (without intercept) on the EC $PM_{2.5}$ concentration as measured by the DustTrak. If adjustment of the HEF settings could indeed compensate for changes in the ambient $PM_{2.5}$ concentration to yield a predictable EC $PM_{2.5}$ concentration, the linear regression would be statistically significant.

e. Graphs were created to demonstrate that other measured HEF parameters remained at target levels during the trials.

3. To test how temperature, relative humidity, and pollutant gas concentrations differed from ambient conditions, graphical comparisons of ambient and EC air delivery pipe conditions were made. In addition, t-tests were carried out on the mean difference between ambient and pipe concentrations for each gas.

Target concentrations

Four target concentrations were set: 0 $\mu g/m^3$ $PM_{2.5}$ (filtered air), 20 $\mu g/m^3$ $PM_{2.5}$, 40 $\mu g/m^3$ $PM_{2.5}$, and 60 $\mu g/m^3$ $PM_{2.5}$. The 0 $\mu g/m^3$ $PM_{2.5}$ (filtered air) target concentration was to be achieved by the addition of a HEPA filter (Wilson, HEPA filter cartridge) just upstream of the EC, between two sections of the chamber air delivery pipe. In the other cases, the concentration was controlled as described previously. Each target concentration was attempted four times, for a total of sixteen trials.

Subjects

Four healthy subjects were recruited into the study to test the suitability of the exposure facility for human studies, and to measure cardiopulmonary responses to controlled concentrations of ambient $PM_{2.5}$. Each subject was inside the exposure chamber for one two-hour trial at each target exposure concentration.

Results

The mean, standard error, and number of observations recorded for each variable can be found in Appendix One. These values were used to test the four hypotheses, using the statistical methods described in the *Materials and Methods* section.

Measures of $PM_{2.5}$ Concentration

The first hypothesis was that independent measures of $PM_{2.5}$ concentration are in good agreement, and thus can provide complementary data on exposure. Two independent measures of $PM_{2.5}$ concentration in the air entering the EC were taken, one with the DustTrak aerosol monitor, the other by gravimetric analysis of filter samples. Since preliminary tests of the facility indicated that the DustTrak aerosol monitor read significantly higher than the mean concentration calculated from the gravimetric analysis of the filter, a correction or calibration factor needed to be applied to the DustTrak data. This was confirmed by a t-test of the mean difference between the uncorrected DustTrak values and the filter values of $PM_{2.5}$ concentration (mean difference of -14.31 $\mu g/m^3$, p=0.0489). Regression of the raw DustTrak data on the filter data (without intercept and excluding filtered air exposures), yielded a regression coefficient of 0.61. This factor was then applied to the measured DustTrak values to give a corrected chamber $PM_{2.5}$ concentration calibrated to filter values, and used in all future calculations. Table 3-1 displays the data, with the DustTrak values corrected.

Correlation analysis of the two measures of mean $PM_{2.5}$ EC concentration yielded a Pearson correlation coefficient of 0.92 (p=0.0001). The mean difference between the two measures of mean EC $PM_{2.5}$ concentration was not significant when the calibration factor was applied (t=0.34, p=0.74).

Two independent measures of ambient $PM_{2.5}$ concentration were also recorded and compared. First, in order to correct for overestimation by the DustTrak, a regression of filter data on DustTrak data was executed with no intercept. The coefficient of the slope was calculated to be 0.83. This factor was then applied to all ambient DustTrak values to provide a corrected measure of $PM_{2.5}$ concentration, calibrated to filter values, and used in all future calculations. Table 3-2 displays the data, with the DustTrak values corrected.

Correlation analysis of the two measures of mean $PM_{2.5}$ concentration yielded a Pearson correlation coefficient of 0.91 (p=0.0001). The difference between the two measures of mean ambient $PM_{2.5}$ concentration was not statistically significant when the calibration factor was applied (t = 0.59, p = 0.57).

Table 3-1. Mean exposure chamber $PM_{2.5}$ concentration

Date	Target Exposure ($\mu g/m^3$)	Chamber $PM_{2.5}$ Concentration -- DustTrak ($\mu g/m^3$)	Chamber $PM_{2.5}$ Concentration -- Filter ($\mu g/m^3$)
Feb. 12, 1998	0	0	6
Feb. 16, 1998	0	0	-13[†]
Feb. 18, 1998	0	0	-16[†]
Mar. 17, 1998	0	0	4
Feb. 26, 1998	20	37	34
Mar. 3, 1998	20	36	23
Mar. 10, 1998	20	38	Not available[*]
Mar. 24, 1998	20	38	38
Mar. 12, 1998	40	51	Not available[*]
Mar. 19, 1998	40	52	Not available[*]
Mar. 31, 1998	40	59	45
Apr. 28, 1998	40	58	90
Mar. 26, 1998	60	93	64
Apr. 2, 1998	60	94	90
Apr. 7, 1998	60	90	124
Apr. 14, 1998	60	93	92

[*] filters were contaminated

[†] negative values are the result of the calculation method used

Table 3-2. Mean ambient $PM_{2.5}$ concentration

Date	Target Exposure ($\mu g/m^3$)	Ambient $PM_{2.5}$ Concentration – DustTrak ($\mu g/m^3$)	Ambient $PM_{2.5}$ Concentration – Filter ($\mu g/m^3$)
Feb. 12, 1998	0	19	26
Feb. 16, 1998	0	18	12
Feb. 18, 1998	0	9	-7[†]
Mar. 17, 1998	0	19	19
Feb. 26, 1998	20	18	20
Mar. 3, 1998	20	32	32
Mar. 10, 1998	20	6	Not available[•]
Mar. 24, 1998	20	9	5
Mar. 12, 1998	40	6	Not available[•]
Mar. 19, 1998	40	15	Not available[•]
Mar. 31, 1998	40	35	43
Apr. 28, 1998	40	12	16
Mar. 26, 1998	60	48	45
Apr. 2, 1998	60	14	8
Apr. 7, 1998	60	17	16
Apr. 14, 1998	60	23	25

[•] filters were contaminated

[†] negative values are the result of the calculation method used

Chamber $PM_{2.5}$ Concentration

The second hypothesis to be tested was that (a) target concentrations could be achieved (b) with good stability (c) using a variable source concentration (ambient air $PM_{2.5}$) (d) by the adjustment of HEF settings. To test whether target concentrations were achieved, both the DustTrak and the filter EC $PM_{2.5}$ concentration values were compared to the target exposure concentration. Pearson correlation coefficients of 0.98 ($p=0.0001$) and 0.92 ($p=0.0001$) were obtained, respectively. However, the mean difference between the corrected DustTrak values and the target exposure was significantly different ($t=5.4$, $p=0.0001$), as was the mean difference

between the filter values and target exposure ($t=2.4$, $p=0.035$). The means of the measured $PM_{2.5}$ were higher than the means of the target $PM_{2.5}$ exposure concentration for both sets of measurements.

To examine the stability of the EC $PM_{2.5}$ concentration during each trial, the coefficient of variation for each trial was compared to that for the ambient air $PM_{2.5}$ concentration. Since more DustTrak data was collected (119 to 124 observations per trial, as compared to only 1 per trial with gravimetric filter analysis) only it was examined for stability. Table 3-3 and 3-4 present the relevant data collected. Excluding filtered air exposures, the coefficient of variation for the EC $PM_{2.5}$ concentration ranged from 3.3% to 28.2%, with a mean of 12.8%. The coefficient of variation for the ambient $PM_{2.5}$ concentration ranged from 7.6% to 38.4%, with a mean of 18.0%. Figures 3-4 to 3-7 illustrate the trials with the best and worst stability in the EC.

To test the effect of adjusting the HEF settings in response to changes in the ambient $PM_{2.5}$ concentration in order to achieve target chamber $PM_{2.5}$ concentrations, several approaches were taken. First, the influence of the source $PM_{2.5}$ on the EC $PM_{2.5}$ concentration was tested. Correlation coefficients for the relationship between the EC and source (ambient) $PM_{2.5}$ concentrations were calculated. Pearson correlation coefficients of 0.32 ($p=0.23$) for the DustTrak data, and 0.18 ($p=0.55$) for the filter data, indicated no correlation between the two. That is, the chamber $PM_{2.5}$ concentration was not directly related to the ambient $PM_{2.5}$ concentration. However, it was expected to be related to a combination of the ambient $PM_{2.5}$ concentration and various HEF settings.

Theoretically, the final EC $PM_{2.5}$ concentration was a function of the following: the $PM_{2.5}$ concentration in the air upstream of the HAPC, and the concentration factor achieved by the HAPC. The $PM_{2.5}$ concentration in the air upstream of the HAPC was determined by the ambient $PM_{2.5}$ concentration and the proportion of the total flow contributed by ambient (as opposed to filtered air) sources. The concentration factor achieved by the HAPC was determined by the ratio of the total flow through the system to the stage 2 minor flow (the sum of the EC air flow rate and the filter sampling flow rate). Therefore the following measured parameters contributed to the EC $PM_{2.5}$ concentration:

Table 3-3. Mean, standard deviation, and standard error of the exposure chamber DustTrak $PM_{2.5}$ concentration

Date	Number of Observations	Mean ($\mu g/m^3$)	Standard Error ($\mu g/m^3$)	Standard Deviation ($\mu g/m^3$)
Feb. 12, 1998	120	0	0	0
Feb. 16, 1998	120	0	0	0
Feb. 18, 1998	120	0	0	0
Mar. 17, 1998	120	0	0	0
Feb. 26, 1998	119	24	0.26	2.8
Mar. 3, 1998	122	23	0.21	2.3
Mar. 10, 1998	120	25	0.32	3.5
Mar. 24, 1998	120	25	0.22	2.4
Mar. 12, 1998	121	33	0.68	7.5
Mar. 19, 1998	122	34	0.23	2.5
Mar. 31, 1998	120	39	0.97	11
Apr. 28, 1998	120	38	0.64	7.0
Mar. 26, 1998	120	61	0.19	2.0
Apr. 2, 1998	120	62	0.63	6.9
Apr. 7, 1998	120	59	0.55	6.0
Apr. 14, 1998	122	61	0.38	4.2
All target = 0 $\mu g/m^3$ trials	4	0	0	0
All target = 20 $\mu g/m^3$ trials	4	37	0.59	1.18
All target = 40 $\mu g/m^3$ trials	4	55	2.08	4.15
All target = 60 $\mu g/m^3$ trials	4	93	0.72	1.44

Table 3-4. Mean, standard deviation, and standard error of the ambient DustTrak $PM_{2.5}$ concentration

Date	Number of Observations	Mean ($\mu g/m^3$)	Standard Error ($\mu g/m^3$)	Standard Deviation ($\mu g/m^3$)
Feb. 12, 1998	124	19	0.61	6.80
Feb. 16, 1998	124	18	0.12	1.37
Feb. 18, 1998	121	9	0.19	2.12
Mar. 17, 1998	121	19	0.21	2.29
Feb. 26, 1998	120	18	0.35	3.81
Mar. 3, 1998	-	32	-	-
Mar. 10, 1998	121	6	0.07	0.73
Mar. 24, 1998	120	9	0.14	1.54
Mar. 12, 1998	122	6	0.11	1.18
Mar. 19, 1998	121	15	0.26	2.9
Mar. 31, 1998	121	35	0.42	4.66
Apr. 28, 1998	120	12	0.42	4.61
Mar. 26, 1998	120	48	0.38	4.19
Apr. 2, 1998	120	14	0.19	2.11
Apr. 7, 1998	120	17	0.46	4.99
Apr. 14, 1998	122	23	0.29	3.16
All target = 0 $\mu g/m^3$ trials	4	16	2.34	4.68
All target = 20 $\mu g/m^3$ trials	4	16	5.65	11.31
All target = 40 $\mu g/m^3$ trials	4	17	6.22	12.44
All target = 60 $\mu g/m^3$ trials	4	26	7.80	15.59

Figure 3-4. Percentage change in exposure chamber $PM_{2.5}$ during the Mar. 26 trial

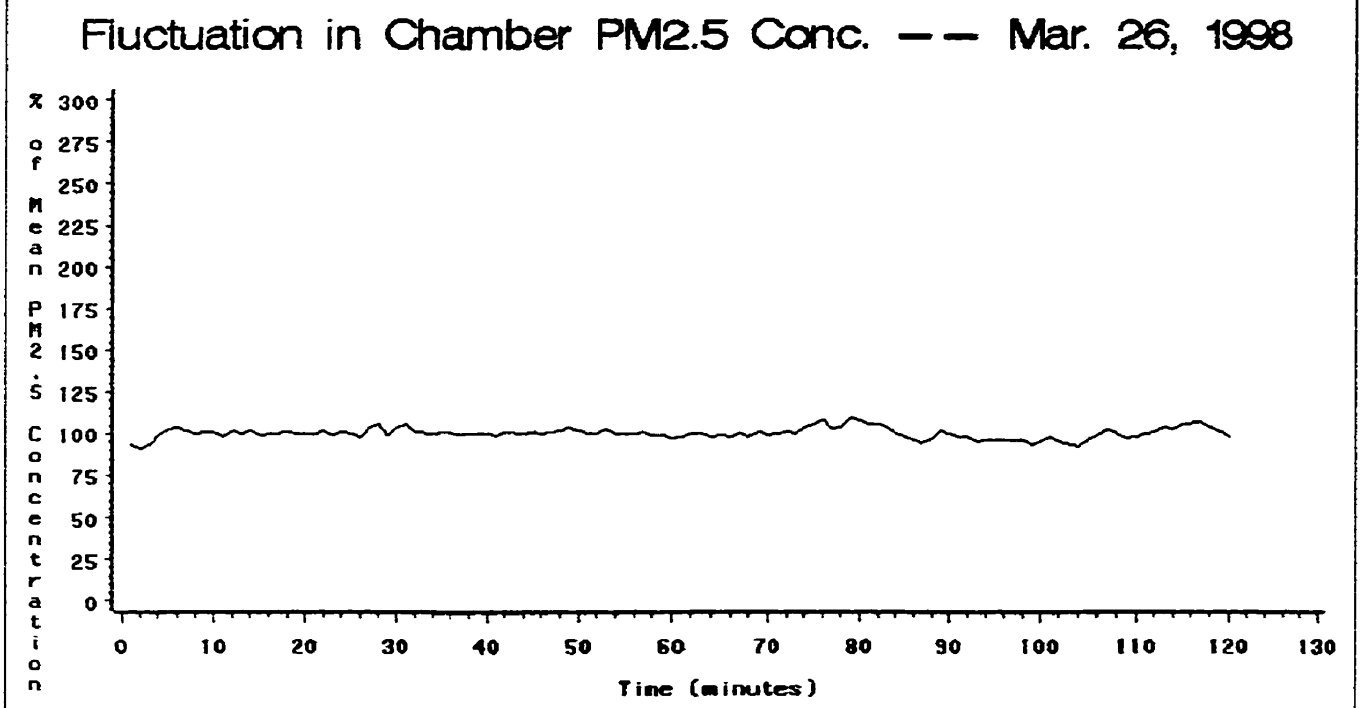


Figure 3-5. Percentage change in ambient $PM_{2.5}$ during the Mar. 26 trial

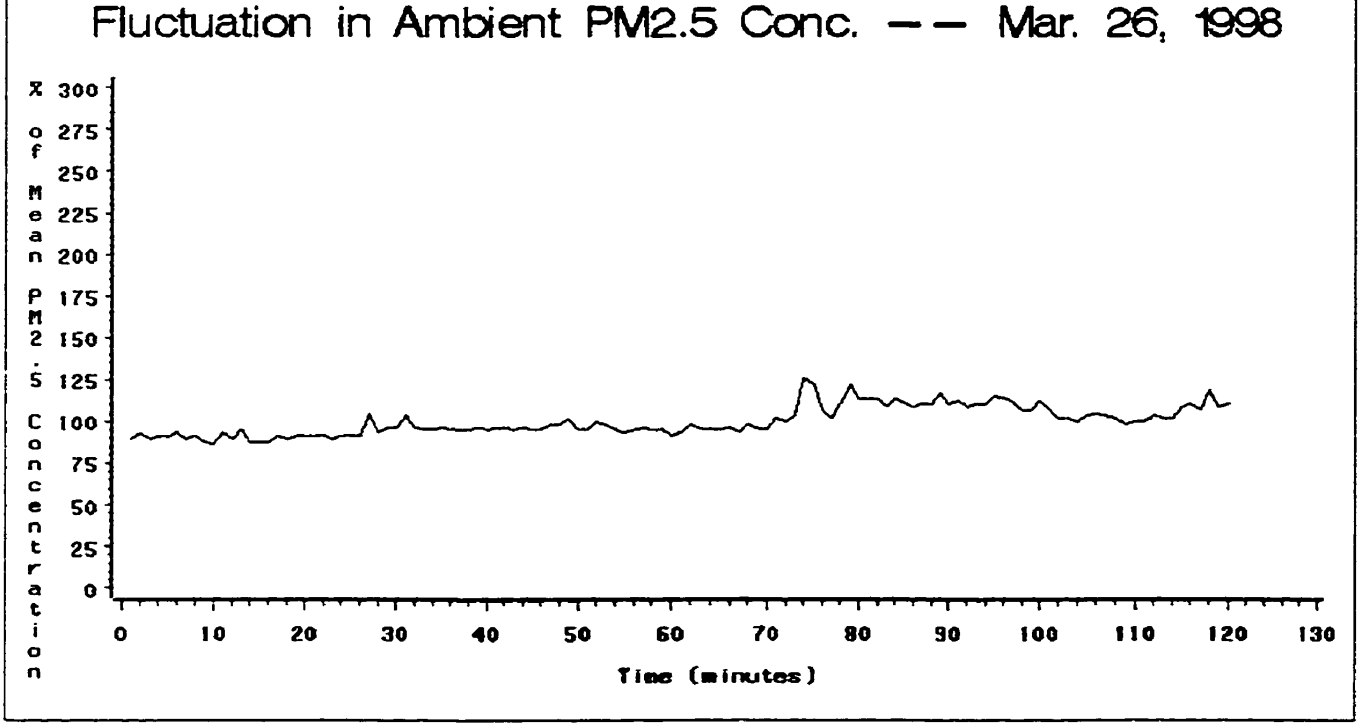


Figure 3-6. Percentage change in exposure chamber $PM_{2.5}$ during the Mar. 12 trial

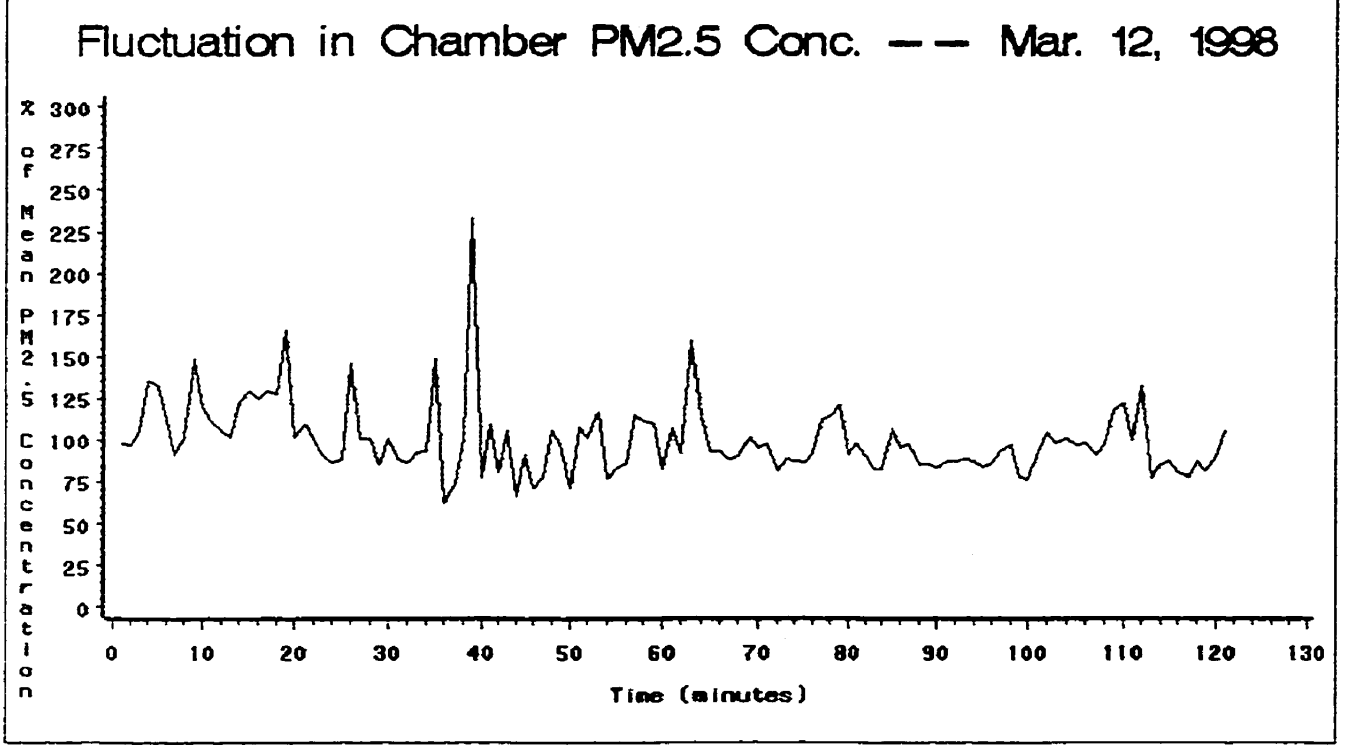
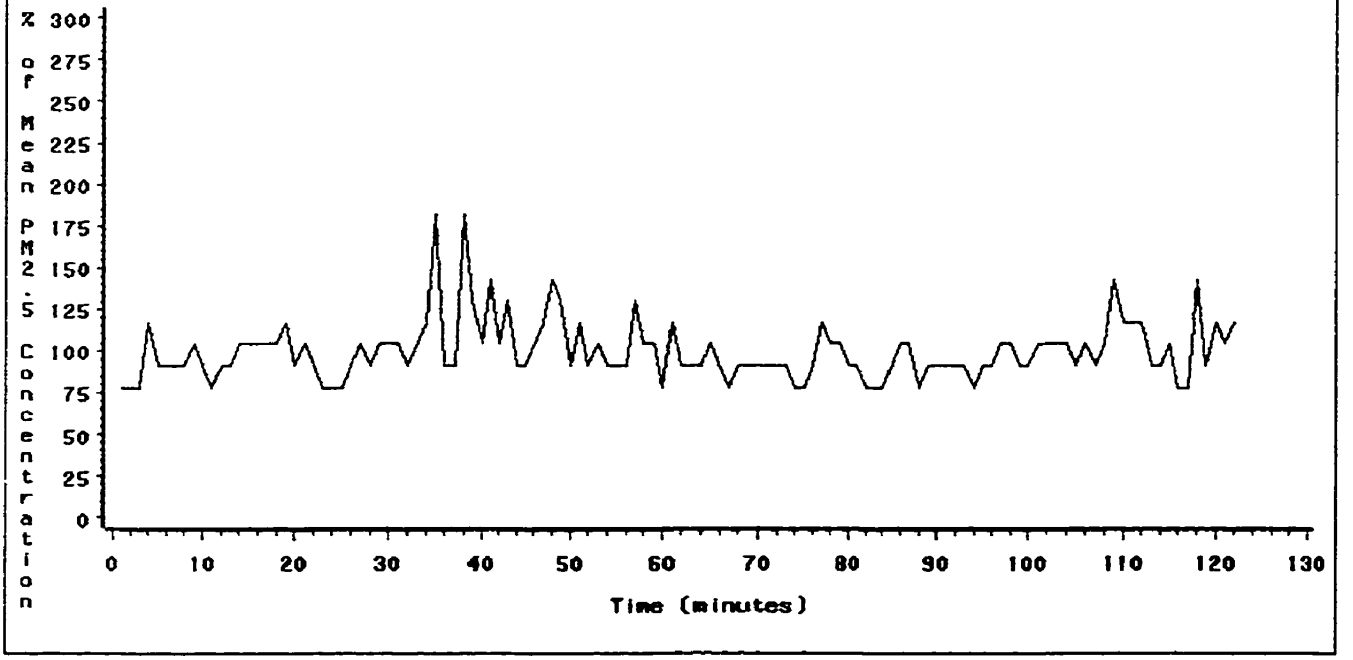


Figure 3-7. Percentage change in ambient $PM_{2.5}$ during the Mar. 12 trial



- ambient (source) $PM_{2.5}$ concentration
- ambient air duct flow rate
- filtered air duct flow rate
- EC air flow rate
- EC filter sampling flow rate

The equation relating these variables can be expressed as follows:

EC $PM_{2.5}$ = Ambient $PM_{2.5}$ x Ambient duct flow/(EC air flow + EC $PM_{2.5}$ sampling filter flow)

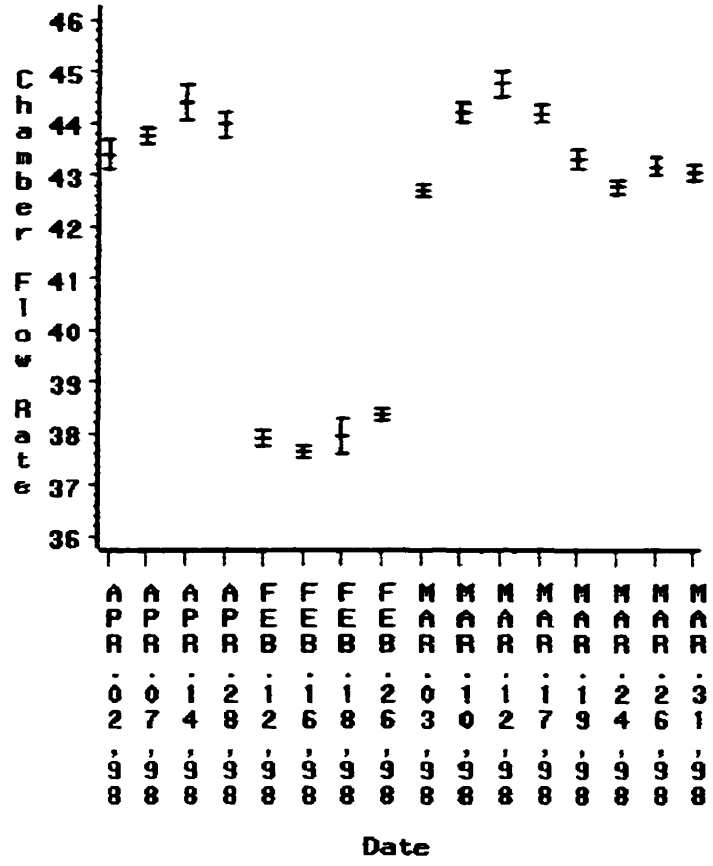
The factors on the right hand side of this equation were all interrelated, since adjustments to flow were made on the basis of changes in ambient $PM_{2.5}$ concentration. Therefore, they were combined into one variable according to the equation above and entered into the following regression model (without intercept) for the EC $PM_{2.5}$ concentration (as measured by the DustTrak aerosol monitor):

Measured EC $PM_{2.5}$ = Estimated EC $PM_{2.5}$ x Regression coefficient

The model yielded an F-value of 88, which was highly significant ($p=0.0001$). The slope of the regression equation was 0.47 ($p=0.0001$), indicating that the estimated $PM_{2.5}$ concentration was approximately double the measured EC $PM_{2.5}$ concentration.

Besides ambient and filtered air duct flow rates, all other HEF settings measured during the exposure trials were to be kept at or near specified targets so that the facility was operating as it was designed. EC air flow rate was set at a target of 40 L/min during four trials, and 45 L/min during the other 12 trials. According to Figure 3-8a and the data in Appendix One, the actual mean flow rate ranged from 38 to 39 L/min when the target was 40 L/min, and from 42 to 45 L/min when the target was 45 L/min. Little fluctuation was observed during each trial, as this parameter was set at the beginning of the trial and not adjusted.

Figure 3-8a. Achievement of target HEF settings -- EC flow rate (L/min)

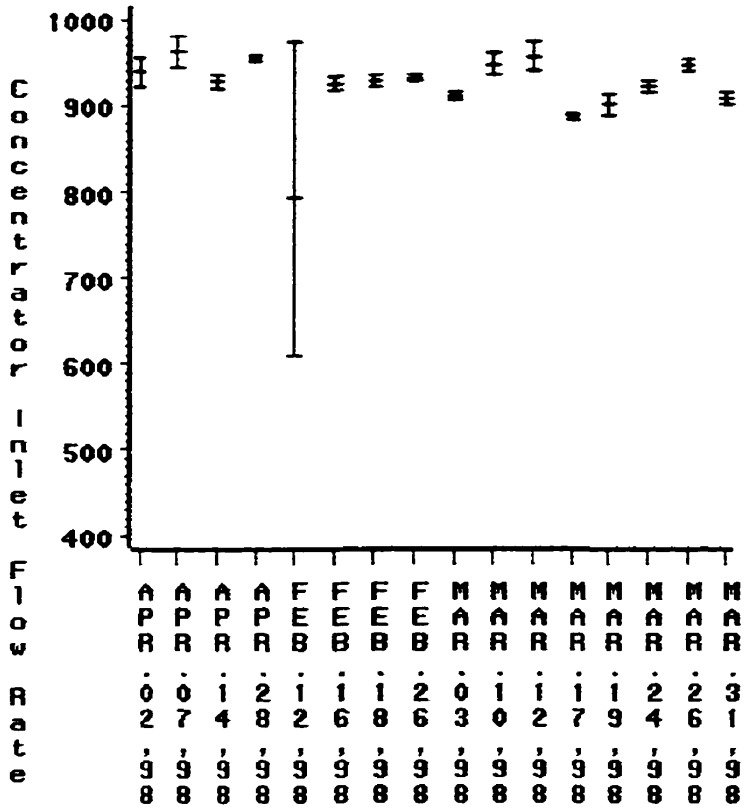


Legend

Bars indicate mean ± standard error

The rate of flow of the air entering the concentrator was set at a theoretical target rate of 1100 L/min, based on the operational major and minor pressures. As Figure 3-8b indicates, the mean measured flow rate ranged from approximately 800 to 1000 L/min. With one exception (the first trial, a filtered air exposure), little fluctuation was seen during each trial, since the pumps creating the air flow were not adjusted.

Figure 3-8b. Achievement of target HEF settings -- Main duct air flow rate (L/min)

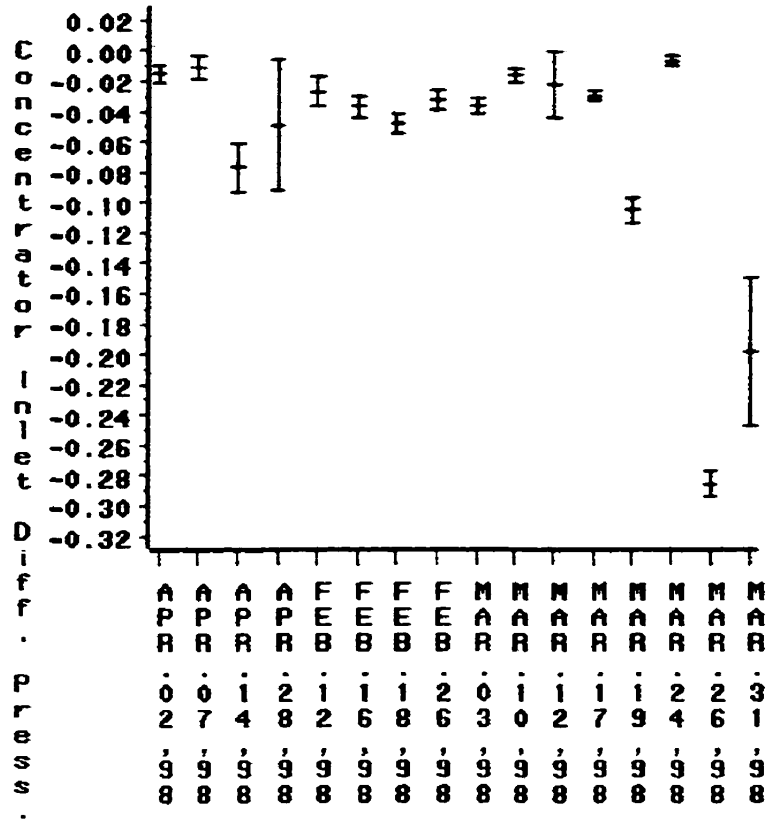


Legend

Bars indicate mean ± standard error

The main duct supplying air to the HAPC was supposed to be maintained at a slightly negative differential pressure of target -0.03 in.w.g. As Figure 3-8c indicates, the actual mean differential pressure ranged from a value of -0.01 to –0.29 in.w.g. Substantial fluctuations were observed both within and between trials.

Figure 3-8c. Achievement of target HEF settings -- Main duct differential pressure (in.w.g.)

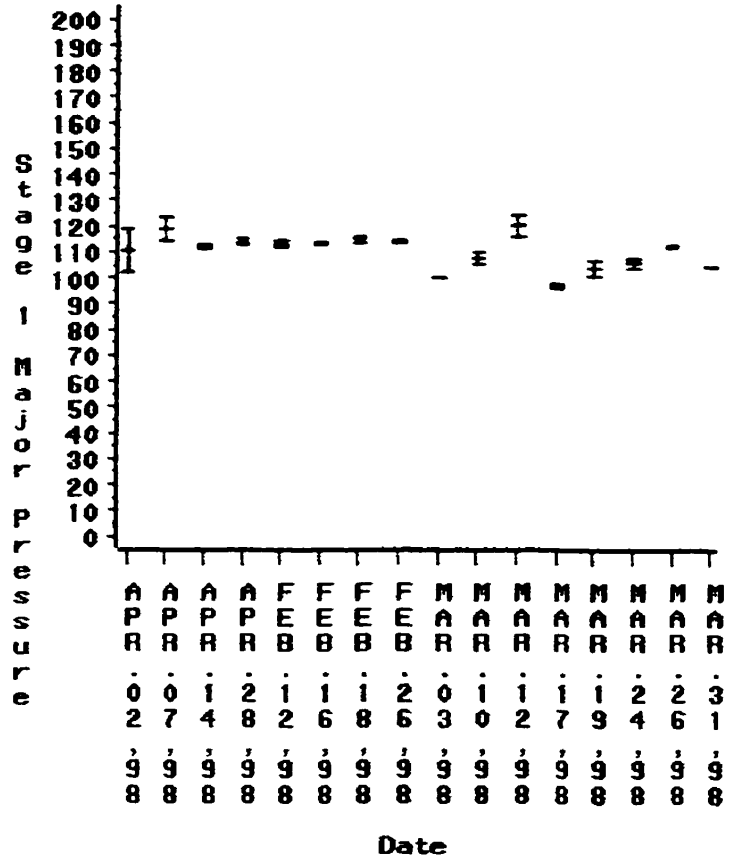


Legend

Bars indicate mean ± standard error

Stage 1 major flow was set so that the measured pressure was 120 in.w.g., based on the specifications provided by the designers of the HAPC. As Figure 3-8d indicates, the actual mean stage 1 major pressure ranged from 97 to 120 in.w.g., due to minor adjustments made to the stage 1 major flow during some of the trials. Nevertheless, little fluctuation was observed between and within trials.

Figure 3-8d. Achievement of target HEF settings -- Stage 1 major pressure (in.w.g.)

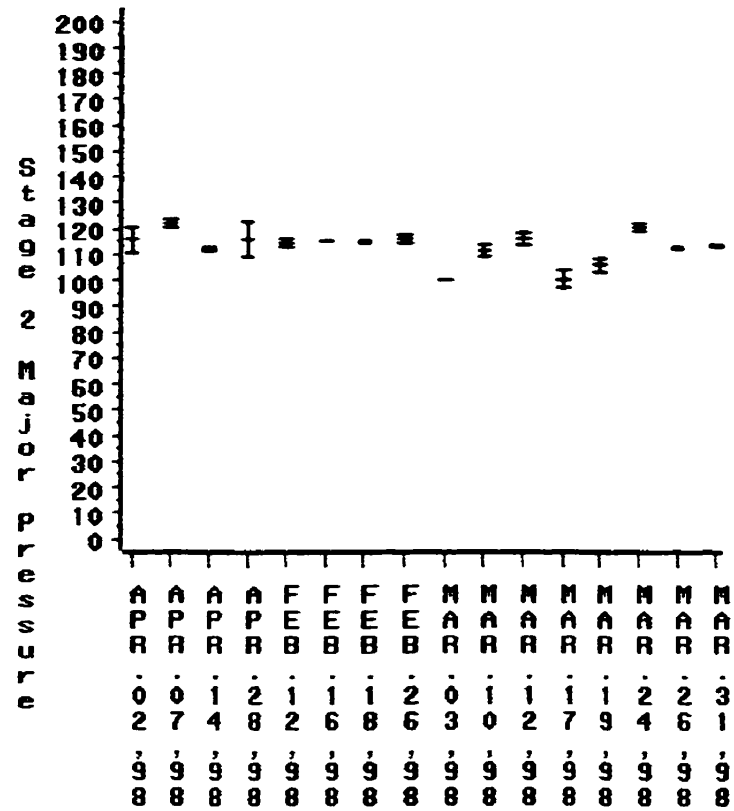


Legend

Bars indicate mean ± standard error

Stage 2 major flow was set so that the measured pressure was 120 in.w.g., based on the specifications provided by the designers of the HAPC. As Figure 3-8e indicates, the actual mean stage 2 major pressure ranged from 100 to 120 in.w.g., due to minor adjustments made to the stage 2 major flow during some of the trials. Again, little fluctuation was observed between and within trials.

Figure 3-8e. Achievement of target HEF settings -- Stage 2 major pressure (in.w.g.)

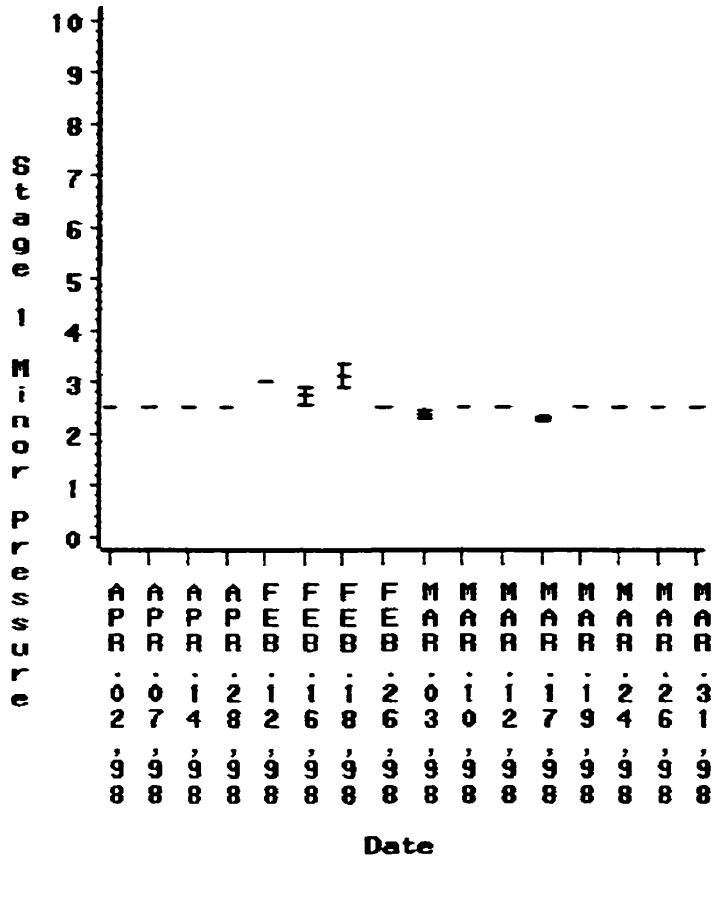


Legend

Bars indicate mean ± standard error

Stage 1 minor flow was set so that the measured pressure was 2.5 in.w.g., based on the specifications provided by the designers of the HAPC, and could only be adjusted indirectly by the adjustment of stage 1 and 2 major flows. As Figure 3-8f indicates, the actual mean stage 1 minor pressure ranged from 2.3 to 3.0 in.w.g. In many cases, no deviation from the target level was observed. In every case, very little or no fluctuation was observed both between and within trials.

Figure 3-8f. Achievement of target HEF settings -- Stage 1 minor pressure (in.w.g.)

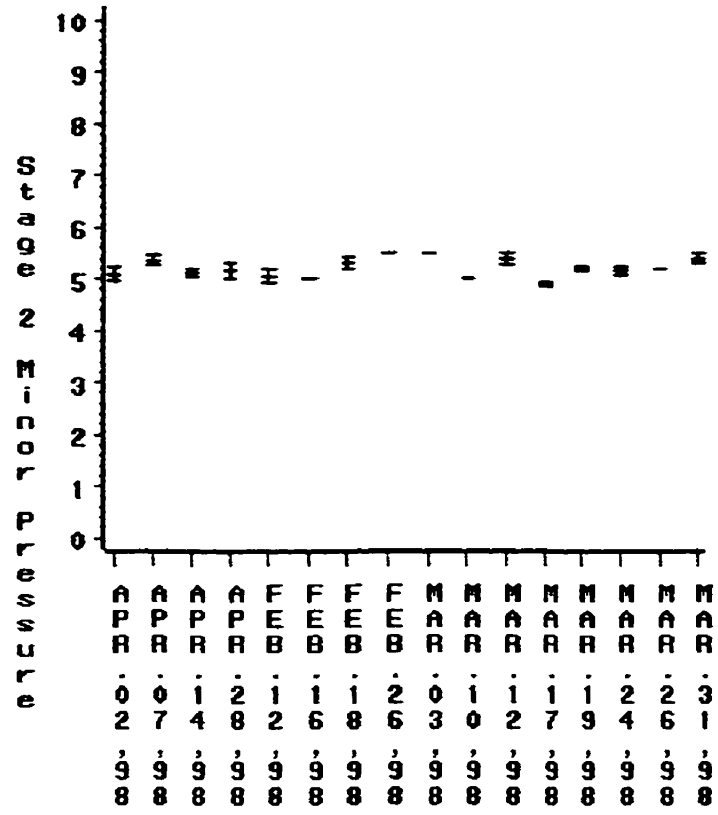


Legend

Bars indicate mean ± standard error

Stage 2 minor flow was set so that the measured pressure was 5 in.w.g., based on the specifications provided by the designers of the HAPC, and could only be adjusted indirectly by the adjustment of stage 1 and stage 2 major flow. As Figure 3-8g indicates, the actual mean stage 2 minor pressure ranged from 4.9 to 5.5 in.w.g. Again, little or no fluctuation was observed both within and between exposure trials.

Figure 3-8g. Achievement of target HEF settings -- Stage 2 minor pressure (in.w.g.)



Legend

Bars indicate mean ± standard error

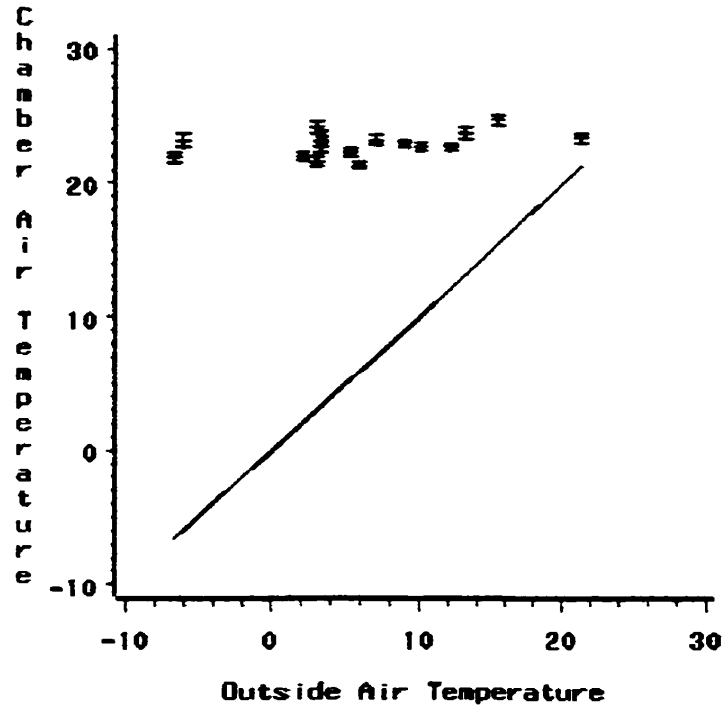
Chamber Environmental Conditions

The third hypothesis to be tested was that temperature can be maintained within a tolerable comfort range and that relative humidity will remain within a tolerable comfort range for the subject during each trial, and that ambient pollutant gas concentrations remain unchanged

in the EC. To test this hypothesis, plots of temperature, humidity, and pollutant gas concentration in the ambient air vs. the EC were made, and t-tests of the mean difference between ambient and EC air delivery pipe gas concentrations were calculated.

As Figure 3-9 illustrates, the air temperature in the EC remained stable despite large changes in the temperature of the ambient air (the source of much of the EC air), and within a reasonable range to ensure the comfort of the subject.

Figure 3-9. Ambient vs. exposure chamber air temperature (° Celsius)

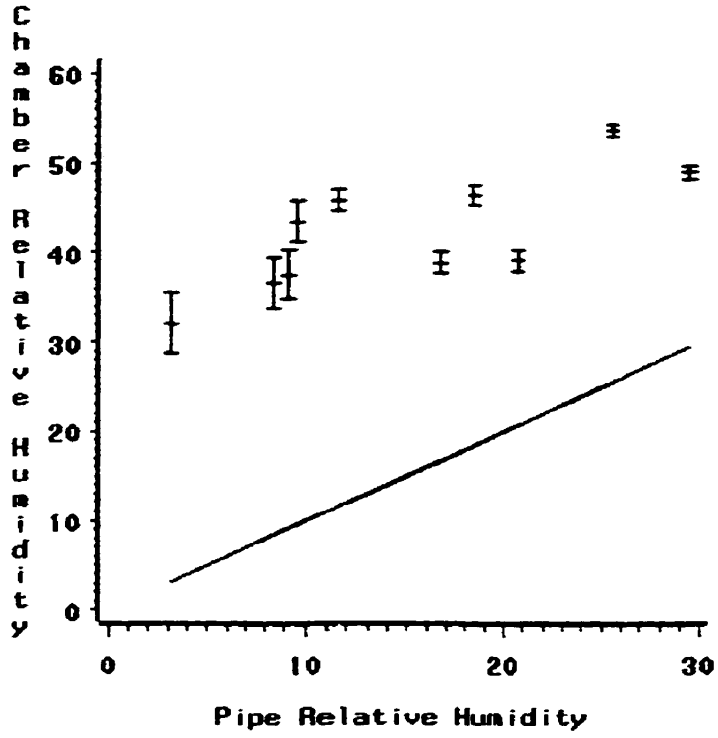


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-10 indicates that relative humidity, although higher in the chamber than in the air delivered to the chamber, remained relatively stable during the trials, and within a reasonable range to ensure the comfort of the subject.

Figure 3-10. EC air delivery pipe vs. EC relative humidity (%)

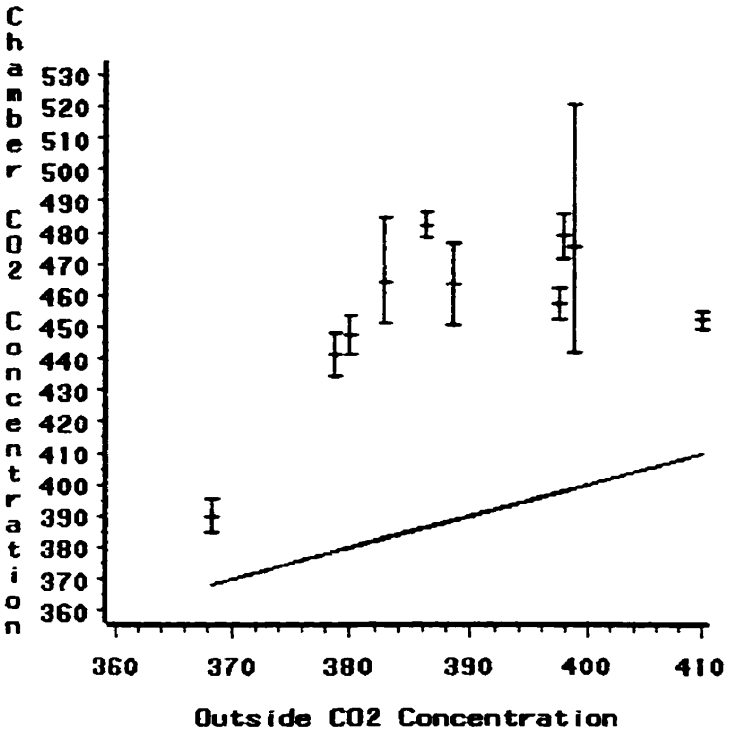


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-11 illustrates that the CO_2 concentration of the air that was delivered to the EC was considerably higher than the ambient air CO_2 concentration. Levels ranged from 370 to 410 ppm in the ambient air, and from 390 to 500 ppm in the EC air delivery pipe. Statistical analysis revealed that pipe CO_2 concentration was significantly higher than ambient (mean difference 70 ppm, $t = 10$, $p = 0.0001$). The pipe to ambient CO_2 ratio was 1.18.

Figure 3-11. Ambient vs. EC air delivery pipe CO_2 concentration (ppm)

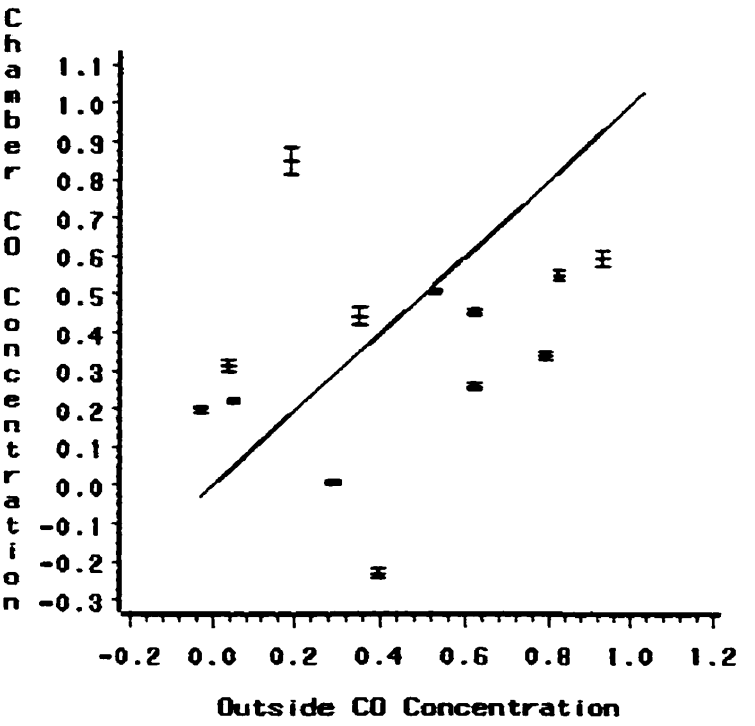


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-12 indicates that the EC air delivery pipe and ambient CO concentrations were quite similar. Mean ambient CO concentration measures ranged from -0.03 to 1.03 ppm, and mean pipe CO concentration measures ranged from -0.23 to 0.85 ppm. Despite the small difference in terms of absolute value, statistical analysis revealed that CO concentration was significantly lower in the pipe than in the ambient air (mean difference 0.17 ppm, $t = -3.7$, $p = 0.0029$). The pipe to ambient CO ratio was 0.69.

Figure 3-12. Ambient vs. EC air delivery pipe CO concentration (ppm)

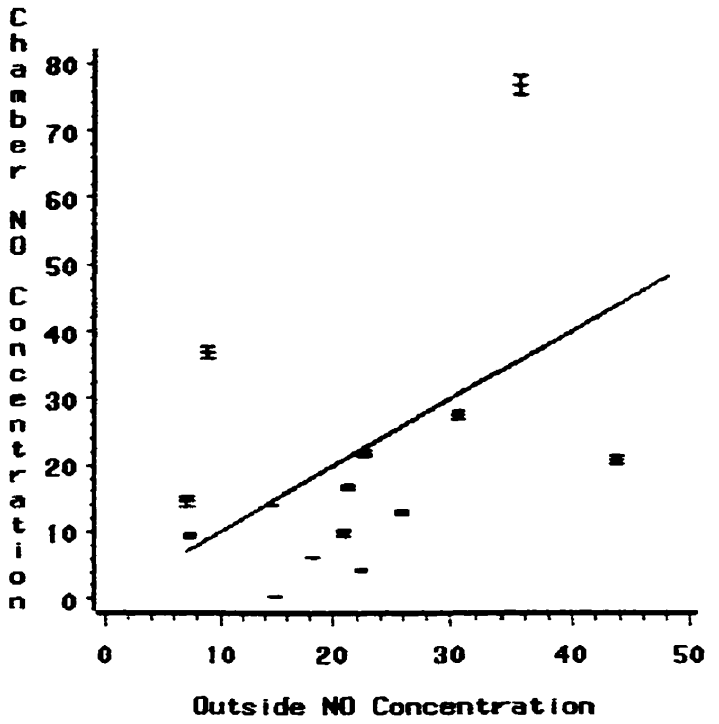


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-13 indicates that ambient and EC air delivery pipe NO concentrations were not very different. Mean ambient NO concentration ranged from 7 to 48 ppb, and mean pipe NO concentration ranged from to 0 to 77 ppb. Statistical analysis revealed no significant difference between pipe and ambient air at $\alpha = 0.05$ ($t = -1.4$, $p = 0.17$). The pipe to ambient NO ratio was 0.81.

Figure 3-13. Ambient vs. EC air delivery pipe NO concentration (ppb)

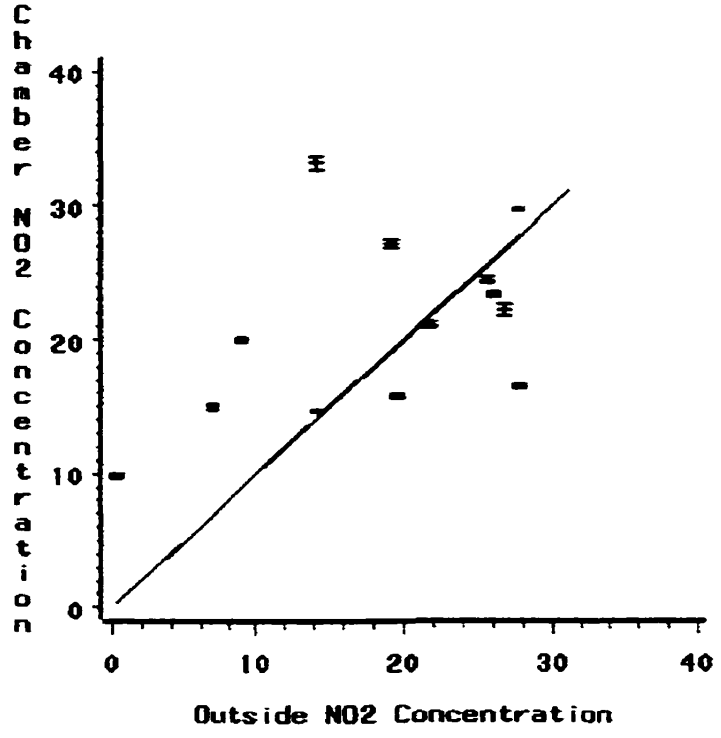


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-14 indicates that ambient and EC air delivery pipe NO_2 concentrations were also not very different. Mean ambient NO_2 concentration ranged from 0 to 31 ppb, and mean pipe NO_2 concentration ranged from to 7 to 33 ppb. Statistical analysis revealed no significant difference between pipe and ambient air at $\alpha = 0.05$ ($t = -1.1$, $p = 0.29$). The pipe to ambient NO_2 ratio was 1.09.

Figure 3-14. Ambient vs. EC air delivery pipe NO_2 concentration (ppb)

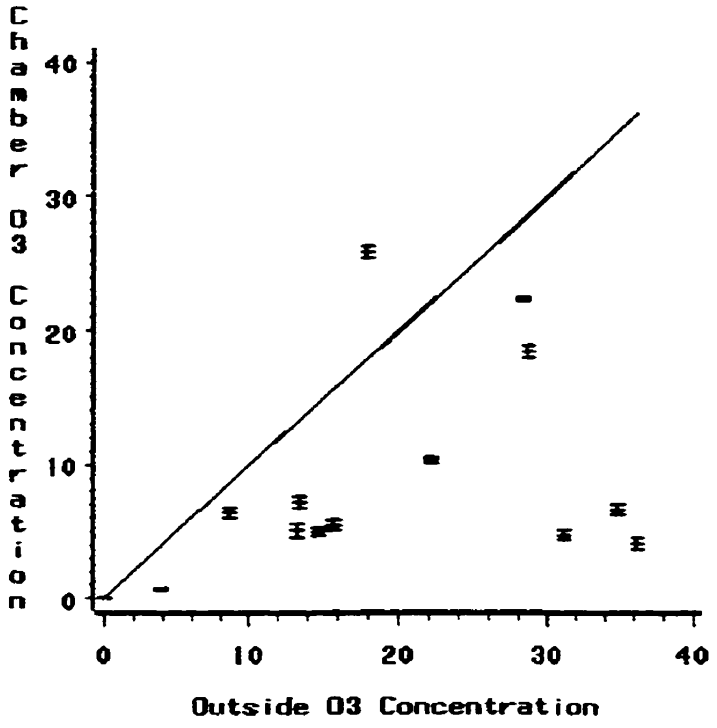


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-15 indicates that EC air delivery pipe O_3 concentration was considerably lower than ambient O_3 concentration in most cases. Mean ambient O_3 concentration ranged from 0 to 36 ppb, and mean pipe O_3 concentration ranged from to 0 to 26 ppb. Statistical analysis revealed that pipe O_3 concentration was significantly lower than ambient (mean difference 9 ppb, $t = -4.3$, $p = 0.0008$). The pipe to ambient O_3 ratio was 0.51.

Figure 3-15. Ambient vs. EC air delivery pipe O_3 concentration (ppb)

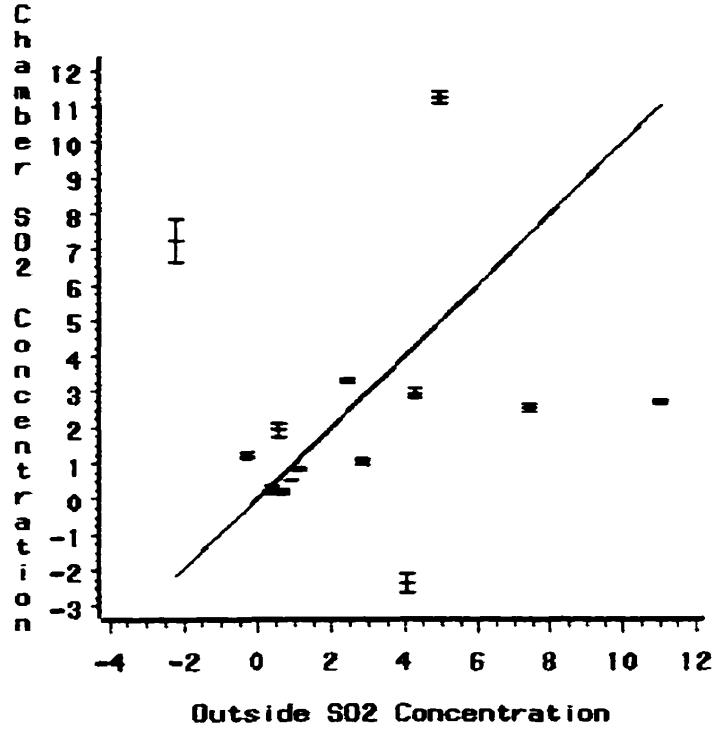


Legend

Bars indicate mean ± standard error Line indicates one to one relationship

Figure 3-16 indicates that ambient and EC air delivery pipe SO_2 concentrations were not very different. Mean ambient SO_2 concentration measures ranged from -2 to 11 ppb, and mean pipe SO_2 concentration measures ranged from to -2 to 11 ppb. Statistical analysis revealed no significant difference between pipe and ambient air at $\alpha = 0.05$ ($t = -0.5$, $p=0.59$). The pipe to ambient SO_2 ratio was 0.82.

Figure 3-16. Ambient vs. EC air delivery pipe SO_2 concentration (ppb)



Legend

Bars indicate mean ± standard error Line indicates one to one relationship

In addition to the reported data, it can be stated that no subject asked to leave at any time during any of the exposures, and no complaints related to the comfort of the chamber conditions were received.

Discussion

Measures of $PM_{2.5}$ Concentration

The results indicated a strong correlation between both measures of $PM_{2.5}$ concentration. Due to the method by which the DustTrak measures PM, the exact relationship between the chamber DustTrak reading and the concentration calculated from the analysis of the filter samples depends on the composition and size distribution of the $PM_{2.5}$ being measured. Therefore, the exact calibration factor used for the DustTrak data was calculated after the fact, based only on the trials reported here. The raw EC DustTrak values were converted to $PM_{2.5}$ concentration values by multiplying the measured values by a factor of 0.61. In the case of ambient $PM_{2.5}$ concentration, the conversion factor calculated was 0.83. The difference between the conversion factors for ambient and EC DustTrak $PM_{2.5}$ suggested that measurement error occurred. Since ambient air sampling yielded filter samples with a collected mass of less than the recommended minimum sample collection (100 μg) in 9 of 11 cases, but EC air sampling yielded samples with a collected mass of less than the recommended minimum in only 4 of 9 cases (due to low target concentrations), it is likely that the calibration factor for the ambient DustTrak values was less accurate than the corresponding factor for the EC DustTrak values.

Although the filter measures of $PM_{2.5}$ concentration could only be calculated after the fact and are considered accurate with minimum sample masses of 100 μg or more, they are the more reliable measure by virtue of the direct mass measurement available. The conversion formulae were therefore necessary to equate the DustTrak values, which had the strength of real-time, continuous and instant measurement, with the filter data. The high correlation between the two measures of chamber $PM_{2.5}$ and the high correlation between the two measures of ambient $PM_{2.5}$ concentration validated the DustTrak measurements. Correcting the raw DustTrak values allowed the reporting of $PM_{2.5}$ concentration with the advantages of both methods, yielding reliable, accurate measurements, assuming that the correction factor was accurate and truly constant. The corrected DustTrak values were therefore used to test whether stable target concentrations were achieved in the EC by the adjustment of HEF settings in response to changes in ambient $PM_{2.5}$.

Chamber $PM_{2.5}$ Concentration

Achievement of target concentrations

The results indicated a strong correlation between target exposure concentration and both measures of EC $PM_{2.5}$ concentration. However, the actual values obtained were significantly different. Extensive testing done prior to these trials suggested that the relationship between the $PM_{2.5}$ reading provided by the DustTrak aerosol monitor and the $PM_{2.5}$ concentration determined by gravimetric analysis was:

DustTrak $PM_{2.5}$ value x 0.4 = actual $PM_{2.5}$ value

It was this relationship that was used during the trials. For example, when the target exposure concentration was 20 $\mu g/m^3$ $PM_{2.5}$, the DustTrak reading that was maintained was 50. Using this relationship, the EC $PM_{2.5}$ concentration as measured by the DustTrak and multiplied by 0.4 would yield a set of values that was not significantly different from the target exposure concentration ($t = 0.41$, $p = 0.69$). However, the calibration factor derived from the trials reported here and applied to the measured DustTrak values was 0.61. For this reason alone, the chamber $PM_{2.5}$ concentrations obtained were significantly higher than the target exposure concentration.

Stability of EC $PM_{2.5}$ concentrations

The EC DustTrak $PM_{2.5}$ concentration measurements were used to assess the ability to maintain a stable exposure concentration in the human exposure facility chamber. The coefficient of variation from the mean EC $PM_{2.5}$ concentration recorded for each trial indicated that the concentrations that were achieved, were also achieved with good stability throughout each two hour trial. In comparison, the ambient $PM_{2.5}$ varied considerably more both within and especially between trials.

Adjustment of HEF settings

A correlation analysis was undertaken to measure the influence of ambient $PM_{2.5}$ on the EC $PM_{2.5}$ concentration. The lack of correlation that was discovered indicated that outside ambient $PM_{2.5}$ alone had little influence on EC $PM_{2.5}$. This was expected, since HEF settings were adjusted to compensate for changes in the ambient $PM_{2.5}$ concentration, in order to

maintain a relatively constant EC $PM_{2.5}$ concentration during each trial.

Ambient $PM_{2.5}$ concentration is continually changing due to changes in output from its sources and to atmospheric conditions. Particles are formed from their various sources, and achieve the position of aerosols, i.e. solids or liquids suspended in the air, by one of two processes: suspension due to grinding or atomisation, or condensation of supersaturated vapours. Supersaturation and condensation may occur as a result of temperature changes, or because gases in the atmosphere react to form compounds with low vapour pressures, which under conditions of supersaturation, nucleate to form particles. The rates of condensation and nucleation change in a complex fashion as atmospheric variables such as temperature and humidity change. Thus changes in atmospheric conditions as well as changes in the quantity of particle sources may result in changes in particle concentration. [9]

In order to maintain a stable $PM_{2.5}$ concentration in the chamber of the human exposure facility, which uses ambient $PM_{2.5}$ as its source, the proportion of total flow entering the HAPC that was from the ambient source was constantly adjusted in response to changes in ambient $PM_{2.5}$ concentration. When ambient $PM_{2.5}$ fell, the proportion of total flow from ambient air was increased, and the proportion of total flow from the filtered air source was decreased. When ambient $PM_{2.5}$ rose, the opposite occurred. The ambient and filtered air flow rates were adjusted by the methods previously described.

A second method of controlling the $PM_{2.5}$ concentration in the chamber of the HEF was to adjust the ratio of total to stage 2 minor flow, which would affect the concentration factor of the HAPC. This was generally done only when changes to the flow rates from ambient and filtered air sources were insufficient to maintain the target $PM_{2.5}$ concentration. The ratio of total to stage 2 minor flow was adjusted by adjusting the stage 1 and/or stage 2 major flow rate, as previously described. Besides these settings, all other measured concentrator parameters were to be kept constant.

Considering the available control methods, the $PM_{2.5}$ concentration in the HEF chamber was, in theory, equal to the product of the $PM_{2.5}$ concentration of the air entering the HAPC and the concentration factor of the HAPC. A model was developed based on this theory. The $PM_{2.5}$ concentration of the air entering the HAPC was estimated by the product of the ambient (source) $PM_{2.5}$ concentration and the proportion of air entering the concentrator from the ambient air

inlet, estimated by the ratio of the ambient duct flow rate to the sum of the ambient and filtered air duct flow rates. The concentration factor of the HAPC was estimated by the quotient of the total flow rate entering the HAPC (the sum of the ambient and filtered air duct flow rates) and the stage 2 minor flow rate, estimated by the sum of the EC flow rate and the EC $PM_{2.5}$ sampling pump flow rate.

Since these parameters were all interrelated, a variable combining all of them according to the relationship described, was entered into a regression model, which was found to be highly significant. This confirmed that the concentrator was operating as it was predicted. However, the value of the slope of the regression line was considerably less than one. A value of one would indicate that the measured EC $PM_{2.5}$ concentration was equal to the estimated EC $PM_{2.5}$ concentration. One or more of the values used to calculate the estimate (ambient DustTrak $PM_{2.5}$, ambient duct air flow rate, filtered air duct flow rate, EC air flow rate, and/or EC $PM_{2.5}$ sampling filter flow rate) was therefore too high, such that the estimate had to be adjusted downward by the application of a coefficient with a value less than one. Since the ambient duct flow rate measured was below the limit of reliable measurement provided by the instruments used, and since the correction factor used to calibrate the ambient DustTrak monitor was based on filter samples of insufficient mass, either of the inputs could be responsible for the error in the estimated EC $PM_{2.5}$ concentration. Furthermore, smaller sampling flows were not included in the equation (gas, DustTrak). Nevertheless, the fact that the regression model was statistically significant verifies that the described relationship does predict the measured EC $PM_{2.5}$ concentration. It can therefore be concluded that adjustment of the HEF settings in response to changes in ambient $PM_{2.5}$ was effective in obtaining the desired target EC $PM_{2.5}$ concentration.

All other measured parameters were supposed to be maintained at or near target levels. However, Figure 3-8a indicated that the EC air flow rate was not constant across all exposures. This was due to an adjustment in the equipment setup during the trials. Initially a target flow rate of 40 L/min was set, in addition to a 10 L/min flow through the particle filter sampler. However, after three filtered air trials and one 20 $\mu g/m^3$ $PM_{2.5}$ target exposure were completed, it was found that not enough material was being collected on the EC filters. In order to compensate, the flow rate through the filter sampler was increased to 15 L/min, and the flow through the chamber to a target rate of 45 L/min. Once this adjustment was made, the chamber flow rate remained constant.

Figure 3-8b indicated that the main duct air flow rate remained constant, as it was designed to do, despite variations in the proportion of flow that was contributed from the ambient and filtered air inlets. The grand mean air flow rate was measured to be 920 ± 10 L/min. This was less than the target flow rate of 1100 L/min. However, the flow rate was calculated indirectly from the Multi-point Sensor differential pressure in the main or common air duct. This sensor was rated for measurement of minimum differential pressures of 0.012 in.w.g., or a flow rate of 1550 L/min, and thus there likely was some error in the flow rate measurement.

Figure 3-8c indicated that the concentrator duct differential pressure was generally maintained at a constant slightly negative pressure. Since pump flow rates were kept constant, the differential pressure was probably most affected by changes in HEPA air filtration system fan speed, which would explain the variability within and between trials.

Figures 3-8d to 3-8g indicated that stage 1 and 2 major and minor pressures were maintained at target levels. The small changes that did occur were likely due to adjustments to the major flows made to achieve the target exposure level, as explained in the *Materials and Methods* section.

Chamber Environmental Conditions

Analysis of the chamber and ambient environmental conditions indicated that temperature and relative humidity in the EC remained at a relatively constant level and within a comfortable range for the subjects while they were in the EC for each two-hour trial. The temperature ranged from 21.3 to 24.7 °C and the relative humidity from 32.0 to 53.7 %. ASHRAE recommends an acceptable range of thermal comfort of approximately 20.3 to 23.6 °C at 50% relative humidity for a person wearing clothing typical of indoor sedentary activity in the winter months.[10] In general, the operating conditions of the EC were within this range.

Analysis of the ambient and the EC air delivery pipe gas concentrations indicated that in the cases of NO, NO_2, and SO_2, the concentrations were not significantly altered from ambient levels. The results for NO_2 agree with the compiled results of many studies that estimate the mean value of the indoor/outdoor NO_2 ratio to be in the range of 0.5 to 1. [11] Estimates for NO are unavailable, as the oxidation of this gas to NO_2 occurs rapidly even at low levels of reactants.[11] For SO_2, estimates of the mean indoor/outdoor ratio range from 0.1 to 0.6 in the

absence of indoor sources, since SO_2 reacts with indoor surfaces and atmospheric ammonia produced by humans.[11] Thus the EC air delivery pipe SO_2 level is slightly higher than would be expected in a normal indoor environment. However, since the direct sources of the chamber atmosphere were ambient air as well as indoor air, this result is not unexpected.

The analysis of pollutant gas concentrations also indicated that the levels of CO_2, CO, and O_3 in the EC air delivery pipe were significantly different from ambient levels. In the case of CO_2, the concentration in the pipe was significantly higher than in the ambient air, probably due to contributions from sources other than the ambient environment. During each exposure trial, there were three to four people in the laboratory running the experiment. Each contributed CO_2 from exhaled breath to the air in the lab, which was the source for the HEPA filtration system and therefore contributed to the added CO_2 in the air delivered to the subject. Nevertheless, the mean level of CO_2 in the air never exceeded 500 ppm, and therefore was well within the comfort range. ASHRAE recommends a minimum air supply per person of 8L/second, which will maintain an indoor CO_2 concentration below 1000 ppm.[10] Thus the EC air delivery pipe CO_2 level gives an indication that adequate ventilation and air quality were maintained in the subject's breathing zone despite the low air supply rate. These results agree with the compiled results of many studies that estimate the mean value of the indoor/outdoor CO_2 ratio to be in the range of 1 to 3.[11]

The concentration of CO in the EC air delivery pipe was not very different from the ambient level in terms of absolute value, but because of the low variability in both measurements, the CO concentration in the pipe was significantly lower from a statistical perspective. Since lab air was the source of the dilution added to the particle-concentrated air, it was not surprising that the CO concentration in the EC air delivery pipe was lower than ambient levels. Since there were few or no significant sources of CO in the lab, the laboratory air (the source of filtered air entering the HEF) would be expected to contain less CO than outside ambient air. In addition, since CO is reducing, the lower concentration in the pipe may be due to some reaction with oxidizing agents within the exposure facility. As a result, the pipe/ambient ratio is slightly lower than the compiled results of many studies that estimate the mean value of the indoor/outdoor CO ratio to be approximately 1 in the absence of indoor sources.[11]

The concentration of O_3 in the EC air delivery pipe was also significantly lower than the

ambient concentration. This may be due to the lower levels of O_3 expected in the indoor air, to the possible removal of O_3 by the HEPA air filtration system, and/or to the possibility that O_3, a powerful oxidant, may have reacted with the metal ductwork at some point of travel between the air inlet and the EC air delivery pipe. The pipe/ambient ratio is slightly higher than the compiled results of many studies that estimate the mean value of the indoor/outdoor O_3 ratio to be in the range of 0.10 to 0.25 in the absence of indoor sources. Again, this is likely due to the fact that the exposure chamber received air directly from both ambient and indoor sources.[11]

The changes in pollutant gas concentration that did occur cannot be considered drawbacks to the functioning of the facility. Since the concentrations of CO and O_3 decreased, they actually reduce the potential for confounding effects on any cardiorespiratory response to $PM_{2.5}$ exposure, and since CO_2 has no effect on respiration at the concentrations measured, it is of no consequence so long as adequate air supply is maintained.

Conclusions

The first hypothesis, that independent measures of $PM_{2.5}$ concentration in the ambient air and in the EC are in good agreement, and can therefore provide complementary data on exposure, was confirmed by the data. The corrected DustTrak and filter data for both the outside ambient and EC $PM_{2.5}$ concentrations were highly correlated, and not significantly different.

Each method has its strengths and weaknesses. The strength of gravimetric filter analysis is that it is a direct mass measurement, and therefore is reliable and accurate if adequate sample mass is collected and the air sampling volume is known. The strength of the DustTrak is that it provides an instantaneous measurement of particle concentration, and this information is required to make adjustments to the HEF to maintain the target level.

The filter analysis provides the most reliable measure of the actual $PM_{2.5}$ concentration because it is a direct mass measurement, but there is a problem of variability that can only be overcome with more trials than the 16 reported here. This is due to the small mass collected during each trial (range of 44 to 243 μg for the EC), often less than the minimum of 100 μg suggested by NIOSH.[8] The DustTrak does not have this variability problem, since it gives instantaneous values and averages every 60 seconds. However, because it is based on the light-scattering properties of the particles it is measuring, it is prone to errors due to differences in

chemical and physical composition from trial to trial. Therefore the DustTrak aerosol monitor, calibrated against the filter data, provides the best measure of $PM_{2.5}$ concentration given the limited number of trials. The two sets of $PM_{2.5}$ concentration measurements are thus complementary, and both are recommended for use in further studies.

The second hypothesis, that stable target $PM_{2.5}$ concentrations can be achieved in the EC using ambient air as the source of particles by adjusting HEF settings, was also confirmed by the data. The DustTrak and filter measures of EC $PM_{2.5}$ concentration were well correlated with target exposure concentration, and were only significantly different from the target exposure concentration because the calibration factor that was applied *a priori* to estimate the actual exposure during each trial was different from the one used in the data analysis after the exposure trials were finished.

The stability of the EC chamber $PM_{2.5}$ concentration varied from trial to trial, but in general, the coefficient of variation indicated that relatively stable concentrations were achieved, especially when compared to the ambient $PM_{2.5}$ concentration, which varied widely between trials and within trials.

There was no significant correlation between the ambient and EC $PM_{2.5}$ concentration, indicating that changes in the $PM_{2.5}$ source concentration did not correspond with changes in the EC $PM_{2.5}$ concentration. This was because changes to various HEF settings compensated for changes in the ambient $PM_{2.5}$ concentration to yield the desired EC $PM_{2.5}$ concentration. It was theorized that ambient $PM_{2.5}$ concentration, the proportion of total flow coming from the ambient duct, and the ratio of total to stage 2 minor flow, combine to determine the final EC $PM_{2.5}$ concentration. A regression analysis relating these factors to the measured EC $PM_{2.5}$ concentration was highly significant, confirming the theory. The primary adjustment was made to the flow rate from the HEPA air filtration system, which in turn affected the proportion of flow from the ambient duct, which in turn affected the $PM_{2.5}$ concentration of the air entering the HAPC, which in turn affected the EC $PM_{2.5}$ concentration. This was found to be quite effective. Since most other parameters can be set prior to exposure with only minor adjustment required during the actual trial, it can be concluded that operation of the human exposure facility is a feasible procedure. The target concentrations could be very closely achieved, without considerable variation, despite large differences in the source concentration between trials, by

adjusting these HEF settings.

The third hypothesis was that EC temperature can be controlled, that relative humidity will remain within comfortable limits, and that ambient pollutant gas concentrations remain unaffected in the EC. All these factors proved not to affect the practicability of the human exposure facility. Temperature and relative humidity remained within a comfortable range for the human subjects. NO, NO_2, and SO_2 levels were not significantly different between the ambient air and the EC air delivery pipe. O_3 and CO concentrations decreased in the chamber, which did not affect the usefulness of the HEF for testing the human health effects of particulate matter exposure, but rather helped to reduce any potential for confounding effects. CO_2 concentration in the EC air delivery pipe did increase significantly, but not sufficiently to create any problems for the chamber environment in terms of safety or air quality, and thus did not affect the usefulness of the HEF either. Accepted standards of 1000 ppm for air quality [10] and 5000 ppm for safety [12] were never exceeded. In all cases, the ratio of pipe to ambient concentration compared closely to the indoor/outdoor ratio determined by previous research.[11]

In this study, no analysis of the $PM_{2.5}$ in the ambient or concentrator samples was undertaken, so possible changes in the composition of the particle mix during the concentration process were not assessed. However, studies of the effects of the HAPC on particle size and composition have been undertaken by Sioutas and colleagues. The conclusions drawn from their research were that ambient particles in the size range 0.1 to 2.5 μm can be concentrated while maintaining the physicochemical characteristics of the ambient mixture.[2]

In one study, this was concluded by the fact that ambient particle concentrations were concentrated by a factor of approximately 26, and ambient sulfate, a subset of the ambient particle mix, was concentrated by a factor of 29, when minor to total flow ratios for three virtual impactors in series were all set to 0.2. When stage III minor flow ratio was set to 0.1, the concentration factor was also 26 for $PM_{2.5}$, and 23 for sulfate. In both cases, the correlation between $PM_{2.5}$ and sulfate concentrations were strong for both the concentrator and ambient conditions. Furthermore, particle losses through the chamber, as measured by sulfate concentration, were less than 10% under all conditions.[2]

In a later study by Sioutas et al. (1995b), the previous findings were confirmed. Particle losses ranged from 10 to 15%, and decreases in the minor to total flow ratio caused the

collection efficiency to decrease and particle losses to increase, which could distort the size distribution of the ambient aerosol. Thus two stages operating at minor flow ratios of 0.20 were recommended.[3]

In the latest study by Sioutas et al. (1997), average concentration factors of 19.4 for fine particulate mass and 19.4 for particulate sulfate were achieved, with no significant differences between the two concentration factors. The concentration factors were in good agreement with predicted values. Tests revealed that the concentration factor was approximately the same for all particle sizes in the range 0.25 to 2.5 μm, and slightly lower for particles smaller than 0.25 μm, and the same for sulfate as for particles in general. Further tests revealed that the concentration factor for ammonium nitrate, one of the most predominant volatile constituents of ambient fine particles, was comparable to the overall concentration factors, indicating that volatile components of the mixture are not lost in the concentration process. [4]

These studies suggest that the size distribution of the ambient aerosol would not have been disturbed in these trials, since the HAPC in this study was operated at minor to total flow ratios of 0.24 (stage I) and 0.21 (stage II), above the recommended level below which collection efficiency and distortion of the size distribution may significantly occur. [3]

In general, the results of this study are encouraging. Target $PM_{2.5}$ concentrations can be achieved in the EC with sufficient accuracy and reasonably little variability. Previous studies of the HAPC have demonstrated that the composition of the particulate matter does not change. This study has demonstrated that the co-pollutant gases from the ambient environment do not accumulate in the HEF, but in some cases are lower, and that temperature and relative humidity in the chamber remain within limits that ensure subject comfort. It can therefore be concluded that the human exposure facility allows accurate studies of the health effects of $PM_{2.5}$ to be undertaken without the troubling issues of weather and co-pollutant influences which make the interpretation of epidemiological research a difficult task, and with an exposure composition that maintains real-world legitimacy, since it is derived from ambient air without modification of the physical and chemical characteristics of the particles of interest.

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Chapter Four: Human pulmonary function response to a controlled exposure to fine urban particulate matter

Introduction

The research reported here was a pilot study, to determine the efficacy of the human exposure facility for controlled exposures to particulate matter, and to examine if healthy subjects would respond adversely to relatively low concentrations of fine ambient particles in a controlled exposure chamber environment. This study was part of a larger project designed to help bridge the gap between epidemiological studies and animal and cell toxicology studies, by examining the effects of controlled exposures of healthy and health-compromised subjects to fine ambient particulate air pollution with and without additional gaseous pollutant exposure, using the new human exposure facility. Four healthy subjects were exposed to four concentrations of ambient fine particles, the only variable being the concentration of $PM_{2.5}$ delivered to the subject. In this way the exposures maintained real-world legitimacy (i.e. ambient $PM_{2.5}$ size and composition maintained) while being more open to study because of the controlled and monitored laboratory conditions. The hypothesis to be tested by the methods described in this chapter was that exposure to $PM_{2.5}$ has a concentration- and time- dependent effect on pulmonary function.

Materials and Methods

Human exposure facility

Ambient air $PM_{2.5}$ was concentrated and delivered to the subject as described in Chapter Three. Air flow within the exposure chamber (EC) was achieved by a pump extracting air out of the chamber at a flow rate of 40 or 45 L/min, causing air to be drawn in from the EC intake pipe to which the delivery mask was attached. The negative pressure created inside the EC by the pump ensured that the air that was inhaled was from the delivery system, and ensured that all exhalation was blown out of the nostril holes in the mask and out into the chamber, and not

rebreathed.

Inside the EC or in the EC air delivery pipe the concentration of $PM_{2.5}$, SO_2, O_3, NO_2, NO, CO, and CO_2, the temperature, and the relative humidity were constantly monitored to ensure no subject discomfort or danger (see Chapter Three).

Subject selection

Four subjects were recruited into the study by advertisement for volunteers on the University of Toronto campus. The criteria for participation in the study were:

1. between 18 and 35 years old
2. never smoked
3. no asthma or other respiratory disease or allergies, or rhinitis
4. no acute respiratory tract infection in the last 3 weeks
5. no inner ear/eardrum disorders or ear problems related to flying
6. all lung function parameters greater than 75% of predicted normal values

Each subject came in on five separate occasions, once for baseline testing, and four times for exposures, to filtered air (FA), and to target exposures of 20, 40, and 60 $\mu g/m^3$ $PM_{2.5}$. On the first visit, subjects were asked to read and sign a consent form approved by an independent University of Toronto Ethics Committee, informing them of the study protocol and possible risks. The recruitment flyer and the consent form can be found in Appendix 3.

Overview of testing protocol

The baseline testing visit consisted of the testing protocol illustrated in Figure 4-1. The testing protocol followed on the actual exposure trial days is illustrated in Figure 4-2. The tests included for this thesis were:

1. Single breath carbon monoxide diffusing capacity, which gives an indication of pulmonary gas exchange efficiency.
2. Body plethysmography, which measures resting lung volume and the resistance to airflow.
3. Minute ventilation, which measures the volume and rate of respiration.
4. Spirometry (using the portable spirometer only), which measures lung volumes and flows.

Figure 4-1. Flow diagram of baseline testing protocol

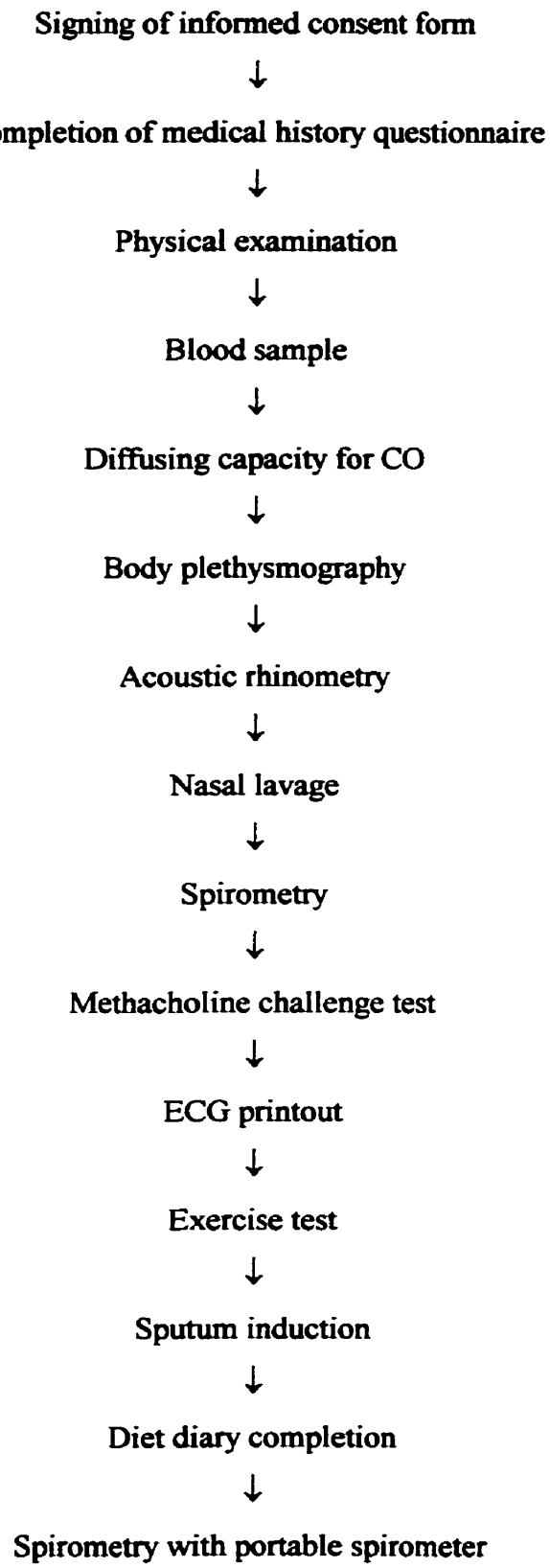
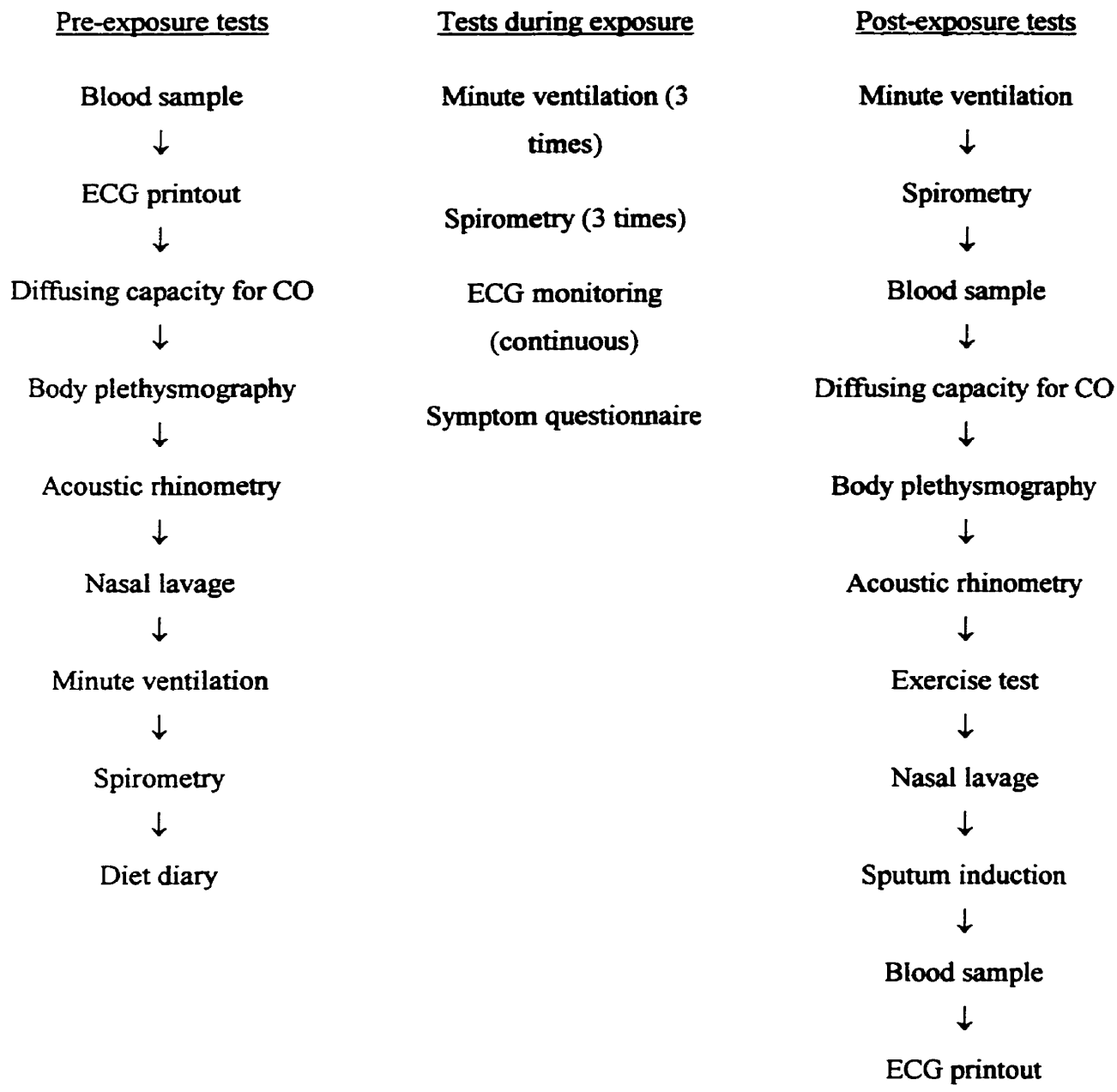


Figure 4-2. Flow diagram of exposure trial testing protocol



Diffusing capacity for carbon monoxide

Single breath carbon monoxide diffusing capacity (DLCO) is a measure of the rate of transfer of CO from inspired gas to pulmonary capillary blood, and is in fact a function of several factors besides diffusion. This test is a good indicator of pulmonary gas exchange efficiency, and therefore is useful in assessing abnormalities that impair alveolar capillary gas transport, such as emphysema or interstitial lung disease.[1,2,3,4]

Because of the complex process that is being measured there is considerable test variability in the measurement of DLCO. To minimize variability, standard equipment was used, and standard procedures were followed.[1] The subject was sitting at rest during the test, had at least 2 hours since his/her last light meal, and had refrained from recent strenuous exercise.[1] At least two tests where the values of DLCO and VC were both within 5% of each other were obtained.[1]

The DLCO test was performed using a Collins Diagnostic System (Collins Medical, Braintree MA). This device had the washout volume set at 1.0 L, and the minimum sample collection volume was 900 ml. Breath hold time was measured by the Ogilvie method, which counts 10 seconds from the beginning of inspiration to the beginning of sample collection. The haemoglobin concentration was set at 14.6 g/dl, and the pre-test carboxyhaemoglobin concentration was set at 0. The values calculated by the test include those listed in Table 4-1.

Table 4-1. Values calculated by the single breath diffusing capacity test.

DLCO	The volume of gas in ml (STPD) that can diffuse across the alveolar-capillary membrane per minute per mmHg of mean pressure gradient
VA	The alveolar volume (BTPS corrected) as derived from the single breath manoeuvre.
DLCO/VA	The rate (BTPS corrected) at which CO diffuses into the blood without regard to volume
VC	The ATPS corrected volume of air inspired from the point of maximum expiration to the point of maximum inspiration.

Body plethysmography

Body plethysmography was performed using a constant-volume, variable pressure plethysmograph (Model 09001, Collins Medical, Braintree MA), a 530 L sealed chamber connected to a console which measures pressure at the mouth proximal to the mouth shutter, inside the chamber, and across a calibrated resistance (the pneumotachograph). The pneumotacograph has a range of ±2 cmH_2O. Chamber pressure is measured with an identical unit. Mouth or transpulmonary pressure is measured with a transducer having a range of ±50 cmH_2O. The measured pressure changes are used to calculate thoracic gas volume and airway resistance using Boyle's law, $P_1V_1 = P_2V_2$.

Thoracic gas volume, or TGV, is the functional residual capacity by the body box method, equal to the volume of gas within the lungs after total relaxation of all respiratory muscles. TGV also includes gas in the intestines and in non-communicating areas in the lungs. Measurement of TGV by body plethysmography was performed following standard procedures.[5] The test was repeated three to six times, with the reported TGV averaged from a minimum of three separate acceptable panting manoeuvres, of which the tangents of the angles measured agree within 10% of the mean.[5]

Airway resistance, abbreviated Raw, is a measure of the resistance of the tracheobronchial tree to the flow of air in the lungs, equal to the ratio of the change in alveolar pressure to the change in flow.[2,3,4] Measurement of airway resistance by body plethysmography was performed following standard procedures.[5] At least 5 pairs of angles were recorded. Measurements were considered acceptable if the calculated values were within 10% of each other.[5]

Minute ventilation

Respiratory minute ventilation testing was performed inside the exposure chamber with the chamber air pump on to create a slight negative pressure, in order to duplicate the conditions during exposure. The tests were performed using a portable ventilation measurement module (Model VMM-401, Interface Associates, Aliso Viejo CA). The instrument uses a turbine type flow transducer and a digital volume transducer, suitable for flow rates up to 3 L/s. Air flowing

through the flow meter bore spins an impeller blade that interrupts a beam of infrared radiation. These interruptions, which are detected by phototransistors, are processed to determine the flow direction, rate, and total volume. The module has a flow range of 0.05 to 5.00 L/s with an accuracy of ± 1.5% and a repeatability of ±0.3% of the original reading. Instrument dead space is 14 ml.

The subject was instructed to put on a noseclip, seal his/her lips around the mouthpiece of the VMM, and breathe normally until a stable value was obtained for both the minute ventilation (Ve), the estimated volume of air exhaled in one minute, and the respiration rate (f), the number of breaths (inhalations and exhalations) taken per minute.

Spirometry

Spirometry measures the volume of air a subject inhales or exhales during standard manoeuvres. Flow, the rate of change of volume as a function of time, is also measured.[2,3,4,6] The subject's breathing moves a volume of air through the spirometer at a varying rate. These volumes and flow rates are measured by the spirometer.

Spirometry was performed inside the exposure chamber with the chamber air pump on to create a slight negative pressure, in order to duplicate the conditions during exposure. Tests were performed using a hand-held portable spirometer (MIR Spirobank Model A23175, Rome, Italy). The spirometer consists of a turbine whose motion is measured by an infrared mini-flow sensor. The motion is converted to flow and volume measurements using correction factors for either body temperature and water pressure (standard correction factor for expiratory manoeuvres, 1.026), or ambient temperature, provided by a semiconductor temperature sensor with a range of 0 to 45 degrees Celsius, for inspiratory manoeuvres. Gas humidity and density do not affect the measurements. The device has a flow range of ±16 L/s BTPS and an accuracy of ±3%. All equipment specifications were within standard guidelines.[6]

Table 4-2 lists the parameters measured by spirometry. The test was administered following standard procedures.[6] A minimum of three acceptable FVC manoeuvres were obtained. Reproducibility was judged by FVC and FEV_1 from successive tests within 5% of each other. The largest FVC, FEV_1, and PEFR were recorded. FEF_{50}, FEF_{25}, FEF_{25-75}, and FEF_{75} were

recorded from the single curve that was acceptable and gave the largest sum of FVC plus FEV_1.[6]

Table 4-2. Pulmonary function parameters measured by spirometry

Parameter	Explanation
FEV_1	Forced expiratory volume in one second, the volume of air exhaled during the first second of the performance of the FVC.
FVC	Forced vital capacity, the maximum volume that can be exhaled with maximally forced effort from a position of maximal inspiration.
PEFR	Peak expiratory flow rate, the maximum rate at which air flows out of the lung during a maximally forced expiration
FEF_{50}	Maximal forced expiratory flow at 50% of vital capacity
FEF_{75}	Maximal forced expiratory flow at 75% of vital capacity
FEF_{25-75}	Average flow during the middle 50% of the FVC manoeuvre (L/s)
FEF_{25}	Maximal forced expiratory flow at 25% of vital capacity

Spirometry tests were repeated in the chamber after 30, 60, 90, and 120 minutes of exposure. In addition, spirometry was performed immediately before and after exposure using a Collins Survey Spirometer (Collins Medical, Braintree MA) connected to a Collins Eagle 1 microprocessor (Collins Medical, Braintree MA) and an X-Y recorder (Hewlett Packard, Palo Alto CA). TLC and RV were calculated indirectly from the TGV values gathered by body plethysmography and the IC and FVC values gathered by the spirometry tests performed using the Collins Survey Spirometer, by the following equations:

TLC = IC (from spirometry) + TGV (from body plethysmography)

RV = TLC - VC (from spirometry)

Inspiratory capacity (IC) is the volume of air that can be inhaled from FRC. Total lung capacity (TLC) is the total volume of air that the lungs can contain. Residual volume (RV) is the

volume of air remaining in the lungs after a complete exhalation.[2,3,4]

Methacholine challenge test

On the day of baseline testing for each subject, a test of the response to methacholine was also performed, to determine the respiratory status of the subject. First, baseline spirometry values were obtained. Next, 3 ml of normal saline were placed in a nebuliser vial and attached to the nebuliser. The subject was instructed to breathe normally from the nebuliser for 2 minutes, while the flow from the nebuliser was set to 0.13 m./min. After 2 minutes, the nebuliser flow meter was turned off, and the nebuliser was removed from the patient. FEV_1 was measured at 30 seconds, 90 seconds, and 180 seconds after the end of the inhalation. Following these steps, methacholine aerosol was administered for two minutes via the nebuliser, beginning at a concentration of 0.03 mg/ml, after which FEV_1 was measured. Subsequent exposures used double the previous concentration of methacholine, while other aspects of the test protocol remained the same. The test was repeated with increasing methacholine concentration until the FEV_1 fell by 20% from the post-diluent (saline) FEV_1 value, or the highest concentration (16.0 mg/ml) had been given. Once the test was completed, the subject was given two puffs of Ventolin, a β_2-agonist, and after 10 minutes the FEV_1 and VC were measured to ensure they were back to baseline levels. The PC_{20}, that concentration of agent that will provoke a fall in FEV_1 of 20%, was calculated from these tests as a measure of airway responsiveness. In normal subjects, such a drop may not be achieved even after the highest dose of methacholine.

Leak check and calibration

All equipment was checked for leaks and calibrated using standard methods before each testing day.[5] Mouthpieces, noseclips, and tubing were sterilized using Metricide, rinsed thoroughly with water, and allowed to air dry at the end of each testing day. Specific procedures were followed for each piece of testing equipment used.

Collins DL system

A leak check of the Collins DL System was performed before each testing day. In addition, the calibration of the bell spirometer used for the DLCO test was checked each day

using a 4 litre syringe, and adjusted if necessary. Furthermore, dessicator columns were checked for saturation, the spirometer water level was maintained, and the potentiometer rod was securely attached to the spirometer bell.

Body plethysmograph

The calibration of the electrical signal amplification which is recorded on the oscilloscope for box pressure, mouth pressure, and flow was checked for accuracy before each testing day. In addition, the operation of the box vent control and the mouth shutter were also tested.

Ventilation measurement module

The ventilation measurement module was tested for accuracy with a 4 L syringe prior to testing on each day. The volume recorded was deemed acceptable if it was within 3% of 4 L. At least three acceptable calibration trials were conducted. The module was cleaned after each testing day with WebCol Alcohol Prep antiseptic isopropyl alcohol pads saturated with 70% isopropyl alcohol.

Spirometer

The spirometer volume measurement was tested for accuracy prior to testing on each day. The recorded FVC and FIVC values (corrected to BTPS and ATPD, respectively) given when the spirometer was attached to a 4 L syringe were recorded and found acceptable if they were within 3% of the appropriate value (4 L * BTPS correction factor of 1.026 for FVC, 4 L * ATPD correction factor for FIVC). The spirometer turbine and sensor were cleaned after each testing day using WebCol Alcohol Prep pads.

Exposure trial order

Since these were the first human exposures carried out using the new facility, for reasons of safety the exposures were performed in increasing order of $PM_{2.5}$ concentration, and only the subject was unaware of the exposure conditions on the test days. At least seven days passed between each subject's exposure days, to avoid the possibility of residual effects from previous

exposures.

Statistics

To test the hypothesis that exposure to $PM_{2.5}$ has a concentration- and time- dependent effect on pulmonary function, the following analyses were performed:

1. Measured pulmonary function values were used to derive the percentage change from pre-exposure by the following formula:

$$\frac{\text{value} - \text{pre-exposure value}}{\text{pre-exposure value}} \times 100\%$$

2. Graphical analyses of all the percentage change values were carried out.

3. Potential confounders were identified by analyzing the correlation of chamber gas concentrations with the percentage change pulmonary function values, and with the $PM_{2.5}$ exposure concentration (filter, DustTrak, and target concentration values). This was done since potential confounders must be related to both exposure and effect. In addition, the pre-exposure gas and particle concentrations were regressed with the pre-exposure pulmonary function values, to determine if ambient exposure prior to testing had an effect on pulmonary function.

4. Analysis of variance was carried out on the percentage change from pre-exposure for all pulmonary function parameters at the four target exposure concentrations.

5. Regression analysis was carried out on the percentage change from pre-exposure for all pulmonary function parameters and the measured $PM_{2.5}$ exposure concentration, for both filter and DustTrak measurements.

6. The mean and 95% confidence interval was calculated for the difference between the percentage change from pre-exposure after the highest exposure and the percentage change from pre-exposure after the filtered air exposure, for each measured pulmonary function variable (PFV). A 95% confidence interval for that difference was then calculated as follows:

$$CI = \text{Difference} \pm t \times se$$

where

CI = confidence interval

Difference = Percentage change in pulmonary function parameter value after the highest exposure condition minus percentage change in pulmonary function parameter value after the filtered air exposure condition

t = critical t value for the 95% confidence interval, where the degrees of freedom of the t distribution is equal to the degrees of freedom of the error term in the analysis of variance for the pulmonary function parameter under consideration

se = standard error, calculated as se = $\sqrt{[MSE * (1/N1 + 1/N2)]}$, where MSE is the mean squared error term from the analysis of variance for the pulmonary function parameter under consideration (an estimate of the variance), N1 is the number of observations recorded for the lowest exposure, and N2 is the number of observations recorded for the highest exposure.

Many of the above statistical tests assume a normally distributed underlying population, and measurement percentages often can be normally distributed. The assumption of an underlying normal distribution usually can be tested, so that if the data were not so distributed, an appropriate transformation could be applied. However, with such a small set of data, one cannot test this assumption, and neither can one be convinced that any particular data transformation is correct. Furthermore, there is insufficient data to perform a non parametric test (e.g. Mann-Whitney test) which makes fewer assumptions about the underlying distribution. Under these circumstances, the above statistical approaches are the most appropriate.

Results

Baseline Results

Seven subjects were recruited and had baseline tests administered. Three were excluded, one because of ECG abnormalities, one because of a difficulty in providing blood samples, and one because of an inability to complete all trials. The four subjects who completed the study consisted of two male and two female university students, all 20 years of age, with normal

pulmonary function and bronchial reactivity, and of adequate fitness to complete the protocol, including the exercise test. Table 4-3 lists the baseline parameter values:

Table 4-3. Baseline Results

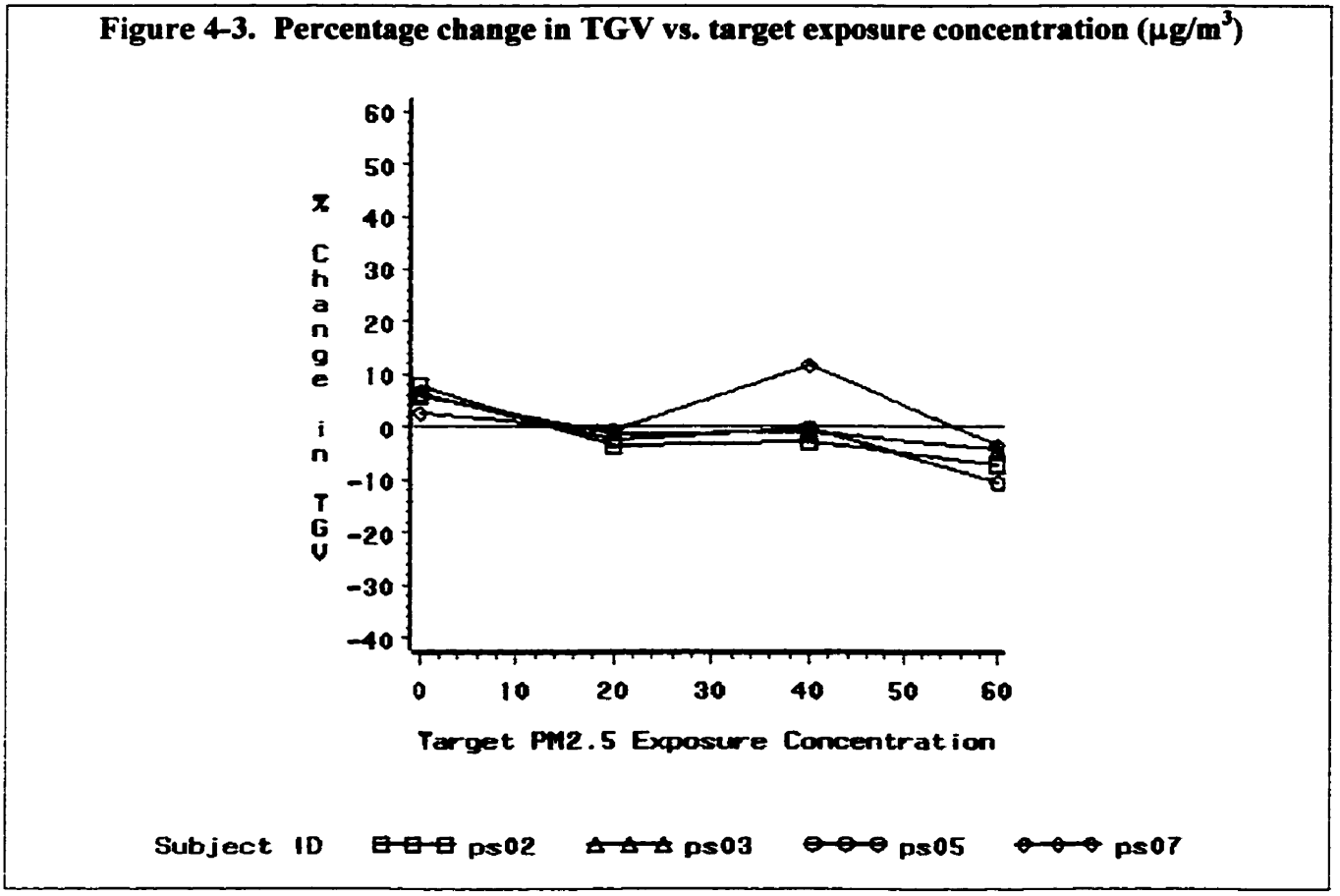
Parameter	PS02	PS03	PS05	PS07
Sex	F	F	M	M
Height (cm)	173	160	177	173
Weight (kg)	74.6	54.0	65.5	69.5
Age (years)	20	20	20	20
DLCO (ml/min/mmHg)	31.57	23.91	32.73	41.62
SB-TLC (L)	6.86	4.60	6.94	6.70
TGV (L)	2.01	2.20	3.21	2.87
Raw (cmH_2O/L/sec)	2.31	1.63	1.51	1.80
TLC (L)	6.05	5.00	6.78	6.67
RV (L)	0.82	1.36	1.08	1.07
FVC (L)	5.01	3.29	5.68	5.50
FEV_1 (L)	3.80	3.21	5.01	4.78
FEV_1/FVC (%)	75.8	97.6	88.2	86
PEFR (L/min)	6.47	6.60	9.35	13.82
FEF_{50} (L/min)	3.75	5.33	5.84	4.68
FEF_{75} (L/min)	1.56	2.95	2.79	2.55
FEF_{25-75} (L/min)	3.26	4.83	5.50	Not recorded
FEF_{25} (L/min)	5.13	5.68	8.93	Not recorded
Response to methacholine	Normal	Normal	Normal	Normal

Exposure results

Graphical analysis of the percentage change from pre-exposure values

The hypothesis to be tested was that exposure to $PM_{2.5}$ has a concentration-dependent or concentration and time-dependent effect on pulmonary function. To test this, each measured post-exposure pulmonary function value was converted to a percentage change from the pre-exposure value. This data can be found in Appendix 2. Figures A2-1 to A2-20 in Appendix 2 illustrate the mean percentage change from pre-exposure in each of the measured PFV's for each subject as a function of the target $PM_{2.5}$ exposure concentration. Only thoracic gas volume showed some indication of a concentration-dependent trend, as Figure 4-3 illustrates. Other pulmonary function parameters either showed little change, or were too variable to make trends easily observable.

Figure 4-3. Percentage change in TGV vs. target exposure concentration ($\mu g/m^3$)



Figures A2-21 to A2-60 in Appendix 2 illustrate the change in minute ventilation and

spirometry parameters over time during each exposure for each subject. In general, FVC, FEV_1, the FEV_1/FVC ratio, and PEFR all remained constant over time during each exposure. The measures of flow, FEF_{25}, FEF_{50}, FEF_{25-75}, and FEF_{75}, and the respiratory minute ventilation parameters, V_E and f, were too variable to make trends easily observable.

Identification of potential confounders

A confounding variable is one that is related to exposure and along with exposure is jointly related to response. In order to identify potential confounding variables a correlation analysis was performed which included all exposure variables ($PM_{2.5}$ and pollutant gas concentrations) and all response variables (pulmonary function parameters). No variables were found which were related to target exposure concentration, or filter or DustTrak measures of $PM_{2.5}$ concentration, and any pulmonary function parameter measured. In addition, a correlation analysis was performed on the ambient $PM_{2.5}$ conditions on the day of testing and pre-exposure pulmonary function. No significant relationships were observed.

Analysis of variance and regression

Analysis of variance (ANOVA) was carried out to determine the effect of target exposure category on each after controlling for inter-subject variability. Regression analysis was also carried out to determine the effect of the actual mean exposure on each variable (using both DustTrak and filter $PM_{2.5}$ values), also after controlling for inter-subject variability. Table 4-4 summarizes the results of these analyses.

Of all the variables tested, only the percentage change in TGV from pre-exposure was found to be significantly related to the target exposure category at $\alpha = 0.05$. Regression analysis using the $PM_{2.5}$ concentration as measured by the DustTrak aerosol monitor confirmed the results obtained by analysis of variance. Tukey's Studentized Range Test (a post hoc statistical test) revealed that the significant difference was between the post-exposure change in TGV after the highest exposure and after the filtered air exposure. The least squares method estimated a mean 5.6% increase from pre-exposure after the filtered air exposure and a mean decrease of 6.4% from pre-exposure after the 60 $\mu g/m^3$ target exposure.

A second analysis of variance was carried out to determine the effects of exposure category, length of exposure, and the interaction of exposure category and length of exposure on each pulmonary function parameter measured by minute ventilation and spirometry tests, also after controlling for inter-subject variability. Table 4-5 summarizes the results of this analysis. No statistically significant relationship was observed for any .

Comparison of the changes in pulmonary function after the highest and filtered air exposures

For each of the measured PFV's, the mean and 95% confidence interval for the difference between the post-exposure change between the highest and lowest (FA) exposures are displayed below in Figure 4-4. Only in the case of TGV was there a significant decrease in the post-exposure change after the highest exposure compared to the filtered air exposure, as indicated by the confidence interval that does not include zero.

Figure 4-4. Difference between change in PFV's after the highest and lowest exposures (%)

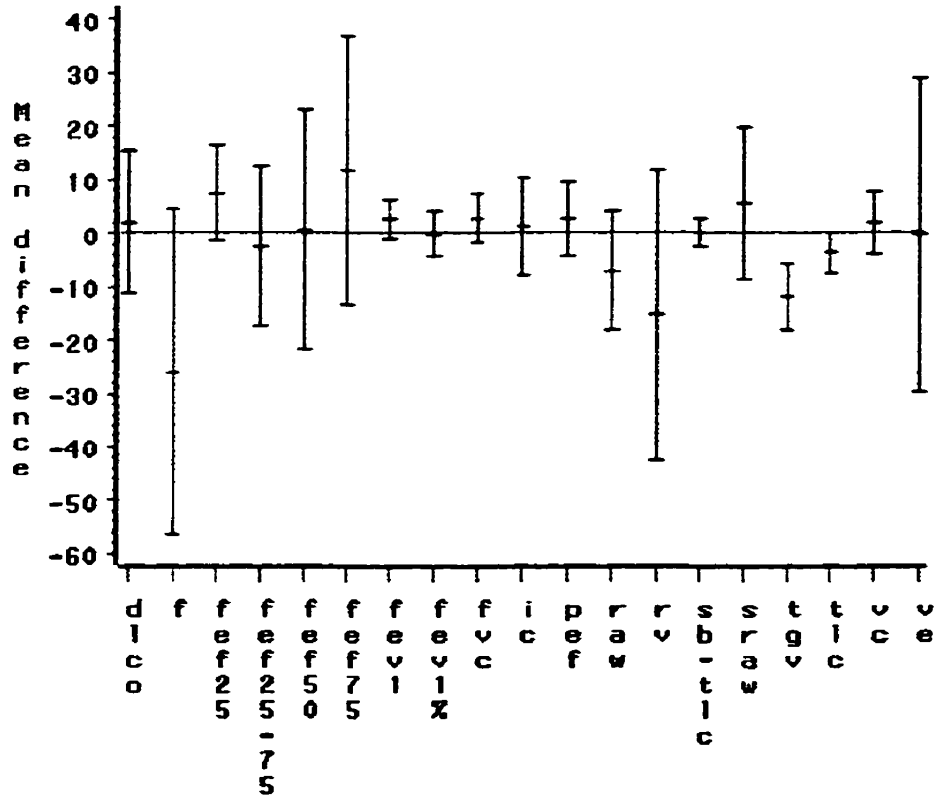


Table 4-4. ANOVA and regression analysis results for the effect of exposure concentration on the percentage change in pulmonary function from pre-exposure

Pulmonary Function Variable	ANOVA		Regression using DustTrak exposure data		Regression using filter exposure data	
	F-value for exposure category	Pr > F	F-value for $PM_{2.5}$ exposure	Pr > F	F-value for $PM_{2.5}$ exposure	Pr > F
VC	0.40	0.76	0.69	0.42	0.78	0.40
FVC	0.63	0.62	2.39	0.15	1.48	0.26
TLC	2.71	0.11	2.84	0.12	2.51	0.15
sb-TLC	0.99	0.44	0.01	0.93	0.34	0.58
TGV	7.02	0.0099	11.92	0.0054	4.18	0.08
IC	0.36	0.78	0.09	0.77	0.06	0.82
RV	1.23	0.35	1.03	0.33	0.36	0.56
FEV_1	2.67	0.11	3.18	0.10	3.05	0.12
FEV_1 / FVC	1.04	0.42	0.02	0.88	0.16	0.70

Table 4-4 (cont'd). ANOVA and regression analysis results for the effect of exposure concentration on the percentage change in pulmonary function from pre-exposure

Pulmonary Function Variable	ANOVA		Regression using DustTrak exposure data		Regression using filter exposure data	
	F-value for exposure category	Pr > F	F-value for $PM_{2.5}$ exposure	Pr > F	F-value for $PM_{2.5}$ exposure	Pr > F
PEF	0.69	0.58	0.98	0.34	0.68	0.43
FEF_{25}	2.91	0.11	1.14	0.31	0.63	0.46
FEF_{50}	1.23	0.36	0.01	0.92	0.02	0.89
FEF_{75}	1.73	0.24	1.23	0.29	1.13	0.32
FEF_{25-75}	1.34	0.32	0.00	0.97	0.00	0.99
Ve	0.50	0.69	0.04	0.84	0.56	0.47
f	1.81	0.22	2.72	0.13	1.20	0.33
Raw	0.98	0.44	2.23	0.16	2.94	0.13
SRaw	0.40	0.75	0.64	0.44	0.08	0.79
D_{LCO}	0.48	0.70	0.04	0.84	0.27	0.62

Table 4-5. ANOVA results for the effect of target exposure concentration and length of exposure on the percentage change in pulmonary function from pre-exposure

Pulmonary Function Variable	Exposure Concentration		Interaction of Exposure Concentration and Length of Exposure	
	F-value	Pr > F	F-value	Pr > F
FVC	0.09	0.97	0.21	0.89
FEV_1	0.50	0.68	1.12	0.35
FEV_1/FVC	0.19	0.90	1.05	0.38
PEFR	0.54	0.66	0.97	0.41
FEF_{25}	1.06	0.37	0.80	0.50
FEF_{50}	0.47	0.71	1.82	0.15
FEF_{75}	0.31	0.82	1.78	0.16
FEF_{25-75}	0.51	0.68	1.72	0.17
V_E	1.10	0.35	0.06	0.98
f	0.23	0.87	1.58	0.20

Discussion

With such a large number of outcome variables the probability of type I statistical error (false positive) is high. On the other hand, the size of the change one might expect to see is very small, thus the probability of type II statistical error (false negative) is also high. In order to reduce these probabilities, a large sample size is required, but this was not feasible. For these reasons, the study cannot rely too heavily on the interpretation of statistically significant results, but rather must rely on the interpretation of confidence intervals and the indications given by individual trends. A wide confidence interval indicates that no conclusions can be drawn safely as to the effect of $PM_{2.5}$ exposure on that variable. A narrow confidence interval indicates that interpretation of the result is possible with some degree of confidence. The criteria for what is 'wide' and what is 'narrow' depends on the normal variability of the parameter under consideration.

When interpreting the data, it is also important to keep in mind that if $PM_{2.5}$ exposure were to have an acute effect, one would expect it would be in the form of airway injury or inflammation, or alveolar injury or inflammation. Airway injury and inflammation could yield obstructive changes characterized by the following changes in pulmonary function:

- increased RV, FRC or TGV, TLC, Raw, and/or SR_{AW}
- decreased VC, FVC, FEV_1, FEV_1/ FVC, PEF, FEF_{75}, FEF_{50}, FEF_{25}, and FEF_{75-25}
- no change in IC, DLCO, Ve, or f

Alveolar injury or inflammation most likely would not produce an effect on lung volume, flow rate, or airway resistance, but could decrease DLCO.

In most cases, there was too much variability in the pulmonary function parameter measurements between trials and between individuals to allow any useful indications of potential effects of particulate matter exposure to emerge. For the variables DLCO, Raw, SRaw, Ve, f, IC, RV, FEF_{50}, FEF_{75}, FEF_{25-75}, and FEF_{25}, the confidence intervals of the mean differences in the post-exposure change between the highest and lowest (FA) exposures was too wide for any interpretation to be made. The individual data was also variable, and no concentration-dependent or concentration and time - dependent trends were observed. In addition, ANOVA and regression analysis revealed no statistically significant exposure or

exposure and time - dependent effects.

In the case of the lung volume parameters VC, FVC, and TLC (measured by two methods), the flow parameters FEV_1 and PEF, and the ratio FEV_1/FVC, little variability was observed. The confidence interval of the mean difference in the post-exposure change between the highest and lowest exposures ranged from ±3 to 7%, and each was within the range of normal variability for that parameter. Therefore it can be stated with some confidence that no effects of particulate matter exposure were observed on these parameters. The individual data also revealed no concentration-dependent or concentration and time – dependent trends. In addition, ANOVA and regression analysis revealed no exposure or exposure and time - dependent effects.

Thoracic gas volume, as measured by body plethysmography, was statistically significantly altered by exposure, with a mean difference of 12% between the highest exposure and the lowest exposure. This is indicated not only by the fact that the confidence interval of the mean difference in the post-exposure change between the highest and lowest exposure conditions did not contain zero, but by the analysis of variance and the post-hoc tests as well. Even though the confidence interval for this difference is relatively small (±6%), caution must be used in interpreting this result. An increase of 5.6% (least squares mean) following the filtered air exposure and a decrease of 6.4% (least squares mean) following the 60 $\mu g/m^3$ $PM_{2.5}$ target exposure both fall within the range of normal variability (approximately ±10% between repeated tests[2,3,4,5]), and thus is of no clinical significance. Keeping in mind the risk of type I statistical error mentioned at the beginning of this section, one can probably dismiss the statistical significance as due to chance. The graphical presentation of the data indicate that the increase from pre-exposure seen following the filtered air exposures, and the decrease seen following the highest exposures, was accompanied by little or no change following the middle exposures.

Comparison to previous research is made difficult because of the uniqueness of the exposure methods and the lack of data on healthy human subjects exposed to particulate matter. Nevertheless, general comparisons can be made on the following bases:

1. Similarity of subjects

2. Similarity of exposure atmosphere
3. Similarity of outcome

Studies in healthy subjects exposed to H_2SO_4 or to other components of fine ambient particulate matter have failed to show changes in pulmonary function, as the studies reviewed in Chapter Two indicate. Thus, these results agree with previous work in healthy subjects, with the exception of the fall in TGV at the highest exposure.

Studies using human subjects and similar exposure atmospheres, i.e., those using ambient particles, have not been published. However, a conference proceeding has been published which indicates that healthy human subjects demonstrated no change in FVC or FEV_1 after two hours exposure (with intermittent exercise) to concentrated ambient particles at exposure levels as high as 500 $\mu g/m^3$.[7] Animal and cell studies using concentrated ambient particles have also been published, and reviewed in Chapter Two. These indicate that exposure may result in increases in pulmonary inflammatory markers, but no functional changes have been observed.

Studies of the respiratory effects of particulate matter exposure which have documented changes in pulmonary function parameters exist as well. As Chapter Two indicates, epidemiological studies have found associations between particulate matter exposure and decreased in PEF, FVC, and/or FEV_1, but generally the populations studied have been children, adult asthmatics, or asthmatic children. Animal studies have documented decreases in FRC in guinea pigs exposed to ZnO, ZnO and SO_2, and to Na_2SO_3, which draw the closest parallels to the changes in TGV demonstrated in this study, but since the species, exposure atmosphere, and testing methods are different, it is impossible to form any conclusions as to the possibility of a common mechanism of effect.

Conclusions

The results reported suggest no adverse human pulmonary function response to $PM_{2.5}$ exposure at target concentrations up to 60 $\mu g/m^3$. No clinically significant changes related to obstruction due to tissue injury or inflammation were seen in any measure of pulmonary function recorded. However, a statistically significant increase in TGV between the 0 and the 60 $\mu g/m^3$ $PM_{2.5}$ target exposures was identified, but this difference was due to a post-exposure increase of

5.6% after the FA exposure, and a post-exposure decrease of 6.3% after the highest exposure, both changes which are within the range of normal variability for thoracic gas volume measurement (± 10%).

Based on the results presented here, it cannot be concluded that a two hour exposure to $PM_{2.5}$ of the same chemical and physical composition as ambient $PM_{2.5}$, at a target concentration as high as 60 $\mu g/m^3$, has an acute adverse effect on pulmonary function. Perhaps the study did not have the statistical power to make such effects observable, or else particulate matter smaller than 2.5 μm or larger than 0.1μm does not represent the particle size responsible for the associations observed in epidemiological studies, or else the study subjects did not reflect the subpopulation that would respond to such exposure. Further research is required to determine which is the case.

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Chapter Five. Accomplishments, Limitations, and Future Directions

Accomplishments

The research previously described has set the groundwork for future research into the acute health effects of fine ambient particulate matter in human subjects. Most importantly, these preliminary trials verified that the new human exposure facility provides a feasible method by which human subjects may be exposed to controlled concentrations of ambient particulate matter in the $PM_{2.5}$ size range.

The sixteen exposure trials reported here demonstrated that the $PM_{2.5}$ concentration in the exposure chamber of the facility can be controlled by coarse methods (i.e. damper positions) prior to exposure, and by fine methods (i.e. filtered air fan speed) during exposure. Problems may occur if the source (ambient) concentration fluctuates too widely during the trial, such that the exposure chamber concentration may vary widely as well. However, despite this limitation, the time-weighted average exposure concentration for the entire two-hour trial remains quite precisely controllable regardless of ambient variability.

Subjects inside the exposure chamber could endure each two-hour trial relatively comfortably. Temperature and relative humidity remained within the recommended range of thermal comfort during all sixteen preliminary trials. No subject asked to leave at any time during any of the exposures. No complaints related to the chamber conditions were received by the experimental staff.

The concentration of pollutant gases, including CO_2, CO, NO_2, NO, O_3, and SO_2, were not affected by the facility in a way that interfered with the exposure trials. In most cases, pollutant gas concentration remained the same, or was only slightly above or below ambient concentrations. In the case of CO_2, levels were increased from ambient concentrations, but not to an extent that would cause subject discomfort or significantly reduce air quality or in any way affect the results of the intended research.

At the levels tested, up to a target exposure concentration of 60 $\mu g/m^3$ $PM_{2.5}$, no clinically significant adverse effects on human pulmonary function were observed. These preliminary results allow new avenues of research to be explored, as suggested below. However, before these opportunities are pursued, some of the limitations of the present research must be evaluated.

Limitations

The major limitations of the present research primarily relate to measurement and to study design, specifically, the limitations of flow measurement techniques, particle measurement techniques, and gas concentration measurement techniques, and the small number of subjects and large number of outcome variables.

The flow measurement techniques used in the present study were inadequate. The Pitot tube measure of HEPA filtration system flow rate and the Multi-point Sensor measures of ambient, filtered air, and mixed air flow rates, are designed for measuring the much larger flow rates that occur in industrial ventilation systems, and their lower limits of detection were often higher than the flows obtained in the present research. The accuracy of the results is therefore highly questionable. Since these trials, a pneumotachometer replaced the Pitot tube measurement of HEPA filtration system flow rate, and it provides a stable reading of flow rate, so that the averaging of 5 measurements is no longer required. This type of flow rate measurement should be used for the ambient, filtered air, and mixed air flow rates as well. Furthermore, stage 1 and 2 major and minor flow rate measurements should be taken as well, so that the actual flow ratios can be calculated to ensure that the HAPC is operated at its optimum settings. If this is not feasible during the exposure trials, at a minimum an equation should be derived based on experimental work which relates the existing pressure gauge readings to a corresponding flow rate, so that an estimate of operating flow rates during exposure trials can be obtained.

A second measurement limitation was the measurement of $PM_{2.5}$ concentration. The DustTrak aerosol monitor is limited due to the light-scattering principles on which it operates. Gravimetric analyses of filter samples are limited by the small mass collected during a two-hour

exposure trial. One way to achieve a greater degree of accuracy would be to have a filter sample in the exposure chamber which is sampled for much longer than the two-hour exposure, so that an adequate mass can be collected. The mean mass concentration recorded from this sample can then be used to derive a calibration factor for the DustTrak aerosol monitor. When this calibration factor is applied, the DustTrak could yield more accurate continuous $PM_{2.5}$ concentration data for the duration of the exposure.

A third limitation is the time-frame for the sampling of pollutant gases. In the experimental design reported here, only one gas at a time was sampled from the exposure chamber air delivery pipe, for a duration of 15 minutes. During this time, the corresponding ambient concentration was not measured. Ideally, it would be best to have continuous monitoring of all pollutant gases both in the ambient air and in the exposure chamber. Of course, this would require twice the equipment, which is the reason it was not done. However, studies which may examine the effects of combinations of particulate matter and pollutant gases will require strict monitoring of pollutant gases, as outlined above.

The study design was also a limiting factor. The repeated-measures design provides a powerful tool for examining effects in a small number of subjects, yet extrapolation to larger populations must be done with extra caution. In the case of the present study, two major limitations have been identified: the small number of subjects, and the large number of outcome variables measured.

The small number of subjects increases the risk of Type II error (false negative), the probability of not rejecting the null hypothesis given that the null hypothesis is not true. In order to reduce the risk of this type of error, either the sample size or the size of the anticipated effect must be increased in order to increase the power of the test. Having established no effects with four healthy subjects at concentrations ranging from 0 to 60 $\mu g/m^3$ $PM_{2.5}$, the next step could be to increase the sample size, the range of exposure concentrations used, or to select a sample from a particularly susceptible subpopulation that may show changes at the exposure levels previously used.

The large number of outcome variables increases the risk of Type I error (false positive), the probability of rejecting the null hypothesis given that the null hypothesis is true. A large

number of outcome variables was necessary in the present study to identify potential outcome variables for upcoming research, e.g., those variables which showed some trend toward a concentration or concentration and time- dependent effect. Since none were identified, future testing could be limited to a few highly reproducible pulmonary function parameters such as FVC and FEV_1, in order to reduce the risk of Type I error. Additionally, potentially more sensitive outcome variables, such as respiratory system changes at the cellular level (e.g. increase in neutrophil concentrations in bronchial fluid), could be measured.

Future Directions

The limitations identified should be improved in further research using the human exposure facility, using the suggestions offered above. In addition, other changes could be made to the monitoring of the system and to the design of future studies.

One recommendation related to $PM_{2.5}$ monitoring would be to monitor the $PM_{2.5}$ concentration of the air just upstream of the HAPC, so that accurate estimates of the particle concentration factor could be calculated. This, combined with more accurate flow monitoring, would allow a predictive equation of exposure chamber $PM_{2.5}$ concentration to be derived based on the model presented in Chapter Three. This would allow more accurate adjustments to be made to the system that would maintain the exposure chamber $PM_{2.5}$ at the target concentration and reduce the variability during the exposure. In the same vein, an equation relating filtered air duct flow rate to HEPA filtration system fan speed would allow accurate adjustment of filtered air flow as soon as ambient $PM_{2.5}$ changes occur, and before the exposure chamber concentration is affected.

Allowing higher $PM_{2.5}$ exposure concentrations would be a logical next step for future studies. However, caution must be used to ensure that the concentrations are still representative of real-life exposures. Due to the weak correlations between ambient $PM_{2.5}$ concentration and personal exposure, perhaps personal $PM_{2.5}$ sampling should be done prior to exposure trials, so that accurate data on real-life exposure is obtained.

Testing of identified at-risk groups, such as the elderly, children, and respiratory-compromised individuals (e.g. asthmatics, COPD patients), should also be considered.

Combinations of different at-risk groups, such as asthmatic children, could also be considered, if deemed acceptable by safety and ethical standards.

Particle exposures with the addition of co-pollutants such as O_3, NO_x, SO_2, and CO, should also be considered. Such exposures could reveal whether $PM_{2.5}$ exposure can potentiate the well documented effects of such pollutants. The human exposure facility can easily be adapted for this purpose, since addition of gases to the air delivered to the exposure chamber could easily be accomplished

Finally, a focus on more subtle respiratory changes should be considered. Pulmonary function testing is a vital component in assessing respiratory health, but the relatively small effects that pollutant exposure can cause may not be detected by such techniques. Changes at the cellular level, such as increases in inflammatory cells and proteins, may be more easily demonstrable, and may provide clues as to the mechanism of $PM_{2.5}$ effects.

Final Conclusions

Previous research demonstrated that the Harvard ambient particle concentrator design utilized in the human exposure facility of the Gage Occupational and Environmental Health Unit allows the concentration of particles in the size range of 0.1 to 2.5 μm, without substantially changing the physical and chemical composition of the particles.[1,2,3] The present study demonstrated that this facility is a feasible method for assessing the human health effects of exposure to fine ambient particulate matter. The filtered air system allowed control over the dilution of the air that is the source of the particles, so that target concentrations could be achieved. Temperature and relative humidity in the exposure chamber remained within comfort levels, so that human subjects could be exposed in two-hour trials. Pollutant gas concentrations were not substantially altered in the exposure chamber, so that they did not interfere with the experimental procedure or results. Healthy subjects exposed to target concentrations of up to 60 $\mu g/m^3$ $PM_{2.5}$ demonstrated no adverse pulmonary function changes in response to the exposure. Improvements to the monitoring of the facility, changes to the sample sizes used, refinement of the respiratory endpoints measured, and the identification of susceptible subjects can now be undertaken so that further research may provide important information on the acute effects of exposure to fine ambient particulate matter.

References

[1] Sioutas C. Koutrakis P. Burton M. "A technique to expose animals to concentrated fine ambient aerosols." Environmental Health Perspectives. 103(2):172-177, 1995 Feb.

[2] Sioutas C. Koutrakis P. Ferguson ST. "Development and evaluation of a prototype ambient particle concentrator for inhalation exposure studies." Inhalation Toxicology. 7:633-644, 1995.

[3] Sioutas C. Koutrakis P. Godleski JJ. Ferguson ST. Kim CS. Burton RM. "Fine particle concentrators for inhalation exposures -- effect of particle size and composition." Journal of Aerosol Science. 28(6):1057-1071, 1997.

Appendix One. Data for Chapter Three

Table A1-1. Summary Filter Data for Ambient and Exposure Chamber PM2.5 Conc.

Date	Target Exposure (ug/m3)	Subject ID	Outside PM2.5 Conc. (ug/m3)	Mixed Air PM2.5 Conc. (ug/m3)	Chamber PM2.5 Conc. (ug/m3)	Estimated Conc. Factor
FEB.12,98	0	ps02	25.83	7.96	5.96	0.75
FEB.16,98	0	ps03	11.69	2.87	-12.98	-4.52
FEB.18,98	0	ps05	-7.40	-1.79	-16.03	8.93
MAR.17,98	0	ps07	19.48	3.08	4.07	1.32
MAR.03,98	20	ps02	31.68	5.73	22.71	3.96
MAR.10,98	20	ps03	.	.	.	.
FEB.26,98	20	ps05	19.86	4.05	33.59	8.29
MAR.24,98	20	ps07	4.67	3.52	38.17	10.86
MAR.19,98	40	ps02	.	.	.	.
MAR.31,98	40	ps03	43.23	18.76	44.79	2.39
MAR.12,98	40	ps05	.	.	.	.
APR.28,98	40	ps07	15.97	11.90	90.08	7.57
APR.02,98	60	ps02	8.11	6.73	89.70	13.33
APR.14,98	60	ps03	24.90	14.64	91.61	6.26
MAR.26,98	60	ps05	45.18	22.59	63.62	2.82

Table A1-1 (continued). Summary Filter Data for Ambient and Exposure Chamber PM2.5 Conc.

Date	Target Exposure (ug/m3)	Subject ID	Outside PM2.5 Conc. (ug/m3)	Mixed Air PM2.5 Conc. (ug/m3)	Chamber PM2.5 Conc. (ug/m3)	Estimated Conc. Factor
APR.07,98	60	ps07	15.58	13.33	123.67	9.28

Table A1-2a. Summary DustTrak Data for Ambient PM2.5 Conc.

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside PM2.5 Obs.	Mean Outside PM2.5 Conc. (ug/m3)	S.E. of the Mean Outside PM2.5 Conc.	Mixed Air PM2.5 Conc. (ug/m3)
FEB.12,98	0	ps02	124	18.75	0.61	5.78
FEB.16,98	0	ps03	124	17.81	0.12	4.37
FEB.18,98	0	ps05	121	9.25	0.19	2.24
MAR.17,98	0	ps07	121	19.11	0.21	3.02
MAR.03,98	20	ps02	.	31.58	.	5.71
MAR.10,98	20	ps03	121	6.28	0.07	4.75
FEB.26,98	20	ps05	120	17.79	0.35	3.63
MAR.24,98	20	ps07	120	9.42	0.14	7.09
MAR.19,98	40	ps02	121	15.03	0.26	6.48
MAR.31,98	40	ps03	121	34.90	0.42	15.15
MAR.12,98	40	ps05	122	6.37	0.11	5.33
APR.28,98	40	ps07	120	11.79	0.42	8.79
APR.02,98	60	ps02	120	13.89	0.19	11.53
APR.14,98	60	ps03	122	23.14	0.29	13.60
MAR.26,98	60	ps05	120	48.24	0.38	24.12
APR.07,98	60	ps07	120	17.04	0.46	14.57

Table A1-2b. Summary DustTrak Data for Exposure Chamber PM2.5 Conc.

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber PM2.5 Obs.	Chamber PM2.5 Conc (ug/m3)	S.E. of the Mean Chamber PM2.5 Conc.	Estimated Conc. Factor
FEB.12,98	0	ps02	120	0.00	0.00	0.00
FEB.16,98	0	ps03	120	0.00	0.00	0.00
FEB.18,98	0	ps05	120	0.00	0.00	0.00
MAR.17,98	0	ps07	120	0.00	0.00	0.00
MAR.03,98	20	ps02	122	35.80	0.32	6.27
MAR.10,98	20	ps03	120	38.24	0.48	8.06
FEB.26,98	20	ps05	119	37.34	0.39	10.29
MAR.24,98	20	ps07	120	38.36	0.34	5.41
MAR.19,98	40	ps02	122	52.26	0.35	8.07
MAR.31,98	40	ps03	120	59.09	1.49	3.90
MAR.12,98	40	ps05	121	51.07	1.04	9.58
APR.28,98	40	ps07	120	58.49	0.98	6.66
APR.02,98	60	ps02	120	94.28	0.97	8.18
APR.14,98	60	ps03	122	93.17	0.59	6.85
MAR.26,98	60	ps05	120	93.45	0.28	3.87
APR.07,98	60	ps07	120	90.91	0.84	6.24

Table A1-3. Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber CO Conc. Obs.	Mean Chamber CO Conc. (ppm)	S.E. of the Mean Chamber CO Conc.
FEB.12,98	0	ps02	207	0.51	0.01
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	.	.	.
MAR.17,98	0	ps07	124	0.20	0.01
MAR.03,98	20	ps02	125	0.34	0.01
MAR.10,98	20	ps03	120	0.07	0.01
FEB.26,98	20	ps05	111	0.26	0.01
MAR.24,98	20	ps07	121	0.22	0.01
MAR.19,98	40	ps02	132	0.45	0.01
MAR.31,98	40	ps03	114	0.31	0.02
MAR.12,98	40	ps05	120	0.01	0.01
APR.28,98	40	ps07	118	0.44	0.02
APR.02,98	60	ps02	120	0.60	0.02
APR.14,98	60	ps03	128	0.55	0.01
MAR.26,98	60	ps05	128	-0.23	0.01
APR.07,98	60	ps07	112	0.85	0.04

Table A1-3 (cont.d). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside CO Conc. Obs.	Mean Outside CO Conc. (ppm)	S.E. of the Mean Outside CO Conc.
FEB.12,98	0	ps02	546	0.53	0.01
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	172	0.29	0.04
MAR.17,98	0	ps07	360	0.35	0.02
MAR.03,98	20	ps02	360	0.79	0.02
MAR.10,98	20	ps03	360	0.04	0.00
FEB.26,98	20	ps05	360	0.39	0.01
MAR.24,98	20	ps07	368	0.19	0.01
MAR.19,98	40	ps02	360	0.62	0.02
MAR.31,98	40	ps03	352	0.82	0.03
MAR.12,98	40	ps05	360	-0.03	0.00
APR.28,98	40	ps07	360	0.63	0.02
APR.02,98	60	ps02	348	0.93	0.03
APR.14,98	60	ps03	360	0.62	0.02
MAR.26,98	60	ps05	360	0.05	0.03
APR.07,98	60	ps07	368	1.03	0.02

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber NO Conc. Obs.	Mean Chamber NO Conc. (ppb)	S.E. of the Mean Chamber NO Conc.
FEB.12,98	0	ps02	180	14.04	0.11
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	120	0.25	0.01
MAR.17,98	0	ps07	124	13.00	0.33
MAR.03,98	20	ps02	120	20.76	0.60
MAR.10,98	20	ps03	116	4.99	0.06
FEB.26,98	20	ps05	112	21.76	0.55
MAR.24,98	20	ps07	112	6.17	0.10
MAR.19,98	40	ps02	120	16.69	0.25
MAR.31,98	40	ps03	164	9.44	0.19
MAR.12,98	40	ps05	120	4.43	0.14
APR.28,98	40	ps07	100	36.75	0.95
APR.02,98	60	ps02	120	27.36	0.60
APR.14,98	60	ps03	124	9.86	0.34
MAR.26,98	60	ps05	120	14.56	0.69
APR.07,98	60	ps07	64	76.68	1.50

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside NO Conc. Obs.	Mean Outside NO Conc. (ppb)	S.E. of the Mean Outside NO Conc.
FEB.12,98	0	ps02	573	14.60	0.15
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	292	22.54	0.22
MAR.17,98	0	ps07	360	18.08	0.50
MAR.03,98	20	ps02	365	43.73	0.74
MAR.10,98	20	ps03	364	7.32	0.12
FEB.26,98	20	ps05	359	22.33	0.74
MAR.24,98	20	ps07	377	8.88	0.14
MAR.19,98	40	ps02	372	21.17	0.47
MAR.31,98	40	ps03	302	20.79	0.65
MAR.12,98	40	ps05	360	7.05	0.12
APR.28,98	40	ps07	378	35.54	0.89
APR.02,98	60	ps02	348	30.57	0.74
APR.14,98	60	ps03	364	14.95	0.39
MAR.26,98	60	ps05	368	25.76	0.56
APR.07,98	60	ps07	416	48.08	1.16

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber NO2 Conc. Obs.	Mean Chamber NO2 Conc. (ppb)	S.E. of the Mean Chamber NO2 Conc.
FEB.12,98	0	ps02	180	14.67	0.13
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	.	.	.
MAR.17,98	0	ps07	124	20.00	0.17
MAR.03,98	20	ps02	120	15.83	0.14
MAR.10,98	20	ps03	116	7.35	0.10
FEB.26,98	20	ps05	112	29.71	0.13
MAR.24,98	20	ps07	112	16.52	0.20
MAR.19,98	40	ps02	120	23.37	0.12
MAR.31,98	40	ps03	164	15.01	0.18
MAR.12,98	40	ps05	120	9.82	0.14
APR.28,98	40	ps07	100	27.17	0.27
APR.02,98	60	ps02	120	21.09	0.25
APR.14,98	60	ps03	124	24.42	0.22
MAR.26,98	60	ps05	120	22.16	0.42
APR.07,98	60	ps07	64	33.22	0.53

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside NO2 Conc. Obs.	Mean Outside NO2 Conc. (ppb)	S.E. of the Mean Outside NO2 Conc.
FEB.12,98	0	ps02	573	14.25	0.10
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	360	0.35	0.01
MAR.17,98	0	ps07	360	19.12	0.20
MAR.03,98	20	ps02	365	19.51	0.10
MAR.10,98	20	ps03	364	6.87	0.09
FEB.26,98	20	ps05	359	26.72	0.26
MAR.24,98	20	ps07	377	14.03	0.15
MAR.19,98	40	ps02	372	25.92	0.17
MAR.31,98	40	ps03	302	25.51	0.32
MAR.12,98	40	ps05	360	8.96	0.10
APR.28,98	40	ps07	378	26.63	0.36
APR.02,98	60	ps02	348	21.67	0.27
APR.14,98	60	ps03	364	27.60	0.26
MAR.26,98	60	ps05	368	27.67	0.26
APR.07,98	60	ps07	416	31.02	0.29

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber CO2 Conc. Obs.	Mean Chamber CO2 Conc. (ppm)	S.E. of the Mean Chamber CO2 Conc.
FEB.12,98	0	ps02	8	482.50	4.53
FEB.16,98	0	ps03	9	457.78	9.54
FEB.18,98	0	ps05	9	412.22	7.60
MAR.17,98	0	ps07	8	482.50	4.12
MAR.03,98	20	ps02	9	452.22	2.78
MAR.10,98	20	ps03	6	390.00	5.16
FEB.26,98	20	ps05	8	487.50	6.75
MAR.24,98	20	ps07	8	463.75	13.08
MAR.19,98	40	ps02	8	456.25	5.32
MAR.31,98	40	ps03	9	478.89	7.35
MAR.12,98	40	ps05	8	472.50	12.36
APR.28,98	40	ps07	8	447.50	6.20
APR.02,98	60	ps02	8	457.50	4.91
APR.14,98	60	ps03	8	441.25	6.93
MAR.26,98	60	ps05	8	447.50	5.26
APR.07,98	60	ps07	7	502.86	17.96

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside CO2 Conc. Obs.	Mean Outside CO2 Conc. (ppm)	S.E. of the Mean Outside CO2 Conc.
FEB.12,98	0	ps02	0	.	.
FEB.16,98	0	ps03	0	.	.
FEB.18,98	0	ps05	0	.	.
MAR.17,98	0	ps07	8	386.25	3.75
MAR.03,98	20	ps02	3	410.00	5.77
MAR.10,98	20	ps03	6	368.33	1.67
FEB.26,98	20	ps05	0	.	.
MAR.24,98	20	ps07	7	388.57	2.61
MAR.19,98	40	ps02	7	382.86	5.65
MAR.31,98	40	ps03	9	397.78	2.22
MAR.12,98	40	ps05	7	382.86	1.84
APR.28,98	40	ps07	8	380.00	6.55
APR.02,98	60	ps02	8	397.50	4.12
APR.14,98	60	ps03	8	378.75	5.81
MAR.26,98	60	ps05	8	398.75	2.27
APR.07,98	60	ps07	8	398.75	3.98

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber O3 Conc. Obs.	Mean Chamber O3 Conc. (ppb)	S.E. of the Mean Chamber O3 Conc.
FEB.12,98	0	ps02	180	0.10	0.00
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	188	22.29	0.14
MAR.17,98	0	ps07	116	5.49	0.35
MAR.03,98	20	ps02	120	0.64	0.05
MAR.10,98	20	ps03	116	19.55	0.36
FEB.26,98	20	ps05	124	5.07	0.48
MAR.24,98	20	ps07	128	18.40	0.46
MAR.19,98	40	ps02	120	4.94	0.28
MAR.31,98	40	ps03	60	4.73	0.35
MAR.12,98	40	ps05	120	25.88	0.47
APR.28,98	40	ps07	120	6.63	0.36
APR.02,98	60	ps02	120	6.43	0.37
APR.14,98	60	ps03	116	10.34	0.26
MAR.26,98	60	ps05	120	4.10	0.38
APR.07,98	60	ps07	124	7.15	0.40

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside O3 Conc. Obs.	Mean Outside O3 Conc. (ppb)	S.E. of the Mean Outside O3 Conc.
FEB.12,98	0	ps02	573	0.09	0.00
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	292	13.20	0.25
MAR.17,98	0	ps07	368	28.59	0.30
MAR.03,98	20	ps02	365	3.94	0.06
MAR.10,98	20	ps03	364	31.05	0.11
FEB.26,98	20	ps05	347	17.87	0.42
MAR.24,98	20	ps07	361	34.86	0.22
MAR.19,98	40	ps02	372	14.65	0.21
MAR.31,98	40	ps03	406	22.05	0.32
MAR.12,98	40	ps05	360	36.16	0.14
APR.28,98	40	ps07	358	13.31	0.36
APR.02,98	60	ps02	348	8.64	0.26
APR.14,98	60	ps03	372	28.27	0.31
MAR.26,98	60	ps05	368	15.70	0.28
APR.07,98	60	ps07	356	10.23	0.26

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber SO2 Conc. Obs.	Mean Chamber SO2 Conc. (ppb)	S.E. of the Mean Chamber SO2 Conc.
FEB.12,98	0	ps02	186	2.94	0.13
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	188	11.23	0.15
MAR.17,98	0	ps07	120	2.52	0.10
MAR.03,98	20	ps02	120	1.04	0.07
MAR.10,98	20	ps03	128	0.45	0.02
FEB.26,98	20	ps05	124	0.20	0.06
MAR.24,98	20	ps07	128	-2.39	0.27
MAR.19,98	40	ps02	120	0.81	0.02
MAR.31,98	40	ps03	128	1.18	0.08
MAR.12,98	40	ps05	120	0.51	0.01
APR.28,98	40	ps07	140	7.24	0.59
APR.02,98	60	ps02	108	0.24	0.11
APR.14,98	60	ps03	120	3.31	0.06
MAR.26,98	60	ps05	120	1.91	0.20
APR.07,98	60	ps07	180	2.71	0.06

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside SO2 Conc. Obs.	Mean Outside SO2 Conc. (ppb)	S.E. of the Mean Outside SO2 Conc.
FEB.12,98	0	ps02	567	4.28	0.06
FEB.16,98	0	ps03	.	.	.
FEB.18,98	0	ps05	308	0.67	0.03
MAR.17,98	0	ps07	364	4.04	0.05
MAR.03,98	20	ps02	365	2.83	0.03
MAR.10,98	20	ps03	352	-0.30	0.06
FEB.26,98	20	ps05	347	0.87	0.04
MAR.24,98	20	ps07	361	-2.18	0.16
MAR.19,98	40	ps02	372	1.13	0.01
MAR.31,98	40	ps03	338	2.42	0.05
MAR.12,98	40	ps05	360	0.53	0.01
APR.28,98	40	ps07	338	11.02	0.51
APR.02,98	60	ps02	360	0.37	0.06
APR.14,98	60	ps03	368	4.96	0.03
MAR.26,98	60	ps05	368	7.42	0.26
APR.07,98	60	ps07	300	3.11	0.05

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber Temperature Obs.	Mean Chamber Temperature (Celsius)	S.E. of the Mean Temperature
FEB.12,98	0	ps02	8	22.25	0.35
FEB.16,98	0	ps03	9	21.56	0.34
FEB.18,98	0	ps05	9	22.67	0.42
MAR.17,98	0	ps07	8	24.14	0.39
MAR.03,98	20	ps02	9	21.29	0.22
MAR.10,98	20	ps03	8	21.94	0.37
FEB.26,98	20	ps05	8	23.19	0.37
MAR.24,98	20	ps07	8	23.43	0.46
MAR.19,98	40	ps02	8	21.93	0.28
MAR.31,98	40	ps03	9	23.40	0.36
MAR.12,98	40	ps05	8	23.20	0.50
APR.28,98	40	ps07	8	22.68	0.21
APR.02,98	60	ps02	8	22.91	0.26
APR.14,98	60	ps03	8	24.69	0.33
MAR.26,98	60	ps05	8	23.71	0.49
APR.07,98	60	ps07	8	22.69	0.26

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Outside Temperature Obs.	Mean Outside Temperature	S.E. of the Mean Outside Temperature
FEB.12,98	0	ps02	8	5.20	0.08
FEB.16,98	0	ps03	9	2.89	0.23
FEB.18,98	0	ps05	9	3.17	0.08
MAR.17,98	0	ps07	8	2.94	0.18
MAR.03,98	20	ps02	9	5.78	0.25
MAR.10,98	20	ps03	8	-6.63	0.21
FEB.26,98	20	ps05	8	6.94	0.15
MAR.24,98	20	ps07	8	3.29	0.20
MAR.19,98	40	ps02	8	2.00	0.00
MAR.31,98	40	ps03	9	21.20	0.15
MAR.12,98	40	ps05	8	-6.13	0.25
APR.28,98	40	ps07	8	12.04	0.03
APR.02,98	60	ps02	8	8.89	0.18
APR.14,98	60	ps03	8	15.36	0.34
MAR.26,98	60	ps05	8	13.10	0.24
APR.07,98	60	ps07	8	10.00	0.25

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber Pipe Temperature Obs.	Mean Chamber Pipe Temperature (Celsius)	S.E. of the Mean Pipe Temperature
FEB.12,98	0	ps02	0	.	.
FEB.16,98	0	ps03	0	.	.
FEB.18,98	0	ps05	0	.	.
MAR.17,98	0	ps07	7	23.49	0.13
MAR.03,98	20	ps02	0	.	.
MAR.10,98	20	ps03	0	.	.
FEB.26,98	20	ps05	0	.	.
MAR.24,98	20	ps07	8	23.08	0.16
MAR.19,98	40	ps02	6	22.32	0.09
MAR.31,98	40	ps03	9	24.80	0.22
MAR.12,98	40	ps05	8	21.73	0.03
APR.28,98	40	ps07	8	24.88	0.16
APR.02,98	60	ps02	8	23.28	0.05
APR.14,98	60	ps03	8	24.91	0.11
MAR.26,98	60	ps05	7	24.61	0.26
APR.07,98	60	ps07	7	24.87	0.12

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	No. of Chamber Relative Humidity Obs.	Mean Chamber Relative Humidity (%)	S.E. of the Mean Relative Humidity
FEB.12,98	0	ps02	8	45.00	1.70
FEB.16,98	0	ps03	9	37.64	1.85
FEB.18,98	0	ps05	9	44.52	1.46
MAR.17,98	0	ps07	8	36.56	2.80
MAR.03,98	20	ps02	9	49.45	1.38
MAR.10,98	20	ps03	8	33.91	2.16
FEB.26,98	20	ps05	8	39.30	2.49
MAR.24,98	20	ps07	8	37.50	2.71
MAR.19,98	40	ps02	8	46.49	1.08
MAR.31,98	40	ps03	9	48.96	0.77
MAR.12,98	40	ps05	8	32.03	3.43
APR.28,98	40	ps07	8	45.86	1.27
APR.02,98	60	ps02	8	53.68	0.65
APR.14,98	60	ps03	8	38.83	1.21
MAR.26,98	60	ps05	8	39.14	1.19
APR.07,98	60	ps07	8	43.44	2.23

Table A1-3 (continued). Summary Data for Ambient and Exposure Chamber Environmental Conditions

Date	Target Exposure (ug/m3)	Subject ID	Number of Chamber Pipe Relative Humidity	Mean Chamber Pipe Relative Humidity (%)	S.E. of the Mean Pipe Relative Humidity
FEB.12,98	0	ps02	0	.	.
FEB.16,98	0	ps03	0	.	.
FEB.18,98	0	ps05	0	.	.
MAR.17,98	0	ps07	7	8.41	0.18
MAR.03,98	20	ps02	0	.	.
MAR.10,98	20	ps03	0	.	.
FEB.26,98	20	ps05	0	.	.
MAR.24,98	20	ps07	8	9.19	0.48
MAR.19,98	40	ps02	5	18.44	0.24
MAR.31,98	40	ps03	9	29.44	1.28
MAR.12,98	40	ps05	8	3.19	0.28
APR.28,98	40	ps07	8	11.49	0.29
APR.02,98	60	ps02	7	25.53	0.59
APR.14,98	60	ps03	8	16.65	0.40
MAR.26,98	60	ps05	8	20.70	0.29
APR.07,98	60	ps07	8	9.63	0.23

Table A1-4. Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	Number of Ambient Inlet Flow Obs.	Mean Ambient Inlet Flow (L/min)	S.E. of Mean Ambient Inlet Flow
FEB.12,98	0	ps02	7	204.25	23.57
FEB.16,98	0	ps03	9	154.74	8.63
FEB.18,98	0	ps05	9	154.74	8.63
MAR.17,98	0	ps07	8	156.37	9.61
MAR.03,98	20	ps02	8	184.01	13.51
MAR.10,98	20	ps03	6	697.49	41.93
FEB.26,98	20	ps05	8	193.05	7.34
MAR.24,98	20	ps07	7	369.81	25.14
MAR.19,98	40	ps02	8	353.80	6.71
MAR.31,98	40	ps03	7	364.02	19.58
MAR.12,98	40	ps05	5	789.43	42.65
APR.28,98	40	ps07	8	464.67	32.64
APR.02,98	60	ps02	8	691.93	39.01
APR.14,98	60	ps03	6	279.43	21.14
MAR.26,98	60	ps05	8	307.12	12.25
APR.07,98	60	ps07	8	628.90	51.56

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	Number of Dilution Inlet Flow Obs	Mean Dilution Inlet Flow (L/min)	S.E. of Mean Dilution Inlet Flow
FEB.12,98	0	ps02	8	458.16	9.10
FEB.16,98	0	ps03	9	475.53	13.37
FEB.18,98	0	ps05	9	483.51	7.72
MAR.17,98	0	ps07	8	831.89	9.86
MAR.03,98	20	ps02	8	833.64	6.39
MAR.10,98	20	ps03	6	225.03	24.10
FEB.26,98	20	ps05	8	753.56	16.37
MAR.24,98	20	ps07	7	121.46	20.24
MAR.19,98	40	ps02	8	467.24	32.89
MAR.31,98	40	ps03	7	474.82	45.87
MAR.12,98	40	ps05	5	153.44	11.74
APR.28,98	40	ps07	8	158.96	26.32
APR.02,98	60	ps02	8	141.70	0.00
APR.14,98	60	ps03	6	195.84	18.99
MAR.26,98	60	ps05	8	307.24	22.33
APR.07,98	60	ps07	8	106.28	23.19

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	Chamber Pump Flow Observations	Mean Chamber Pump Flow (L/min)	S.E. of the Mean Chamber Pump Flow
FEB.12,98	0	ps02	8	37.91	0.03
FEB.16,98	0	ps03	9	37.65	0.02
FEB.18,98	0	ps05	9	37.95	0.11
MAR.17,98	0	ps07	8	44.19	0.04
MAR.03,98	20	ps02	9	42.71	0.03
MAR.10,98	20	ps03	8	44.21	0.04
FEB.26,98	20	ps05	8	38.36	0.03
MAR.24,98	20	ps07	8	42.77	0.03
MAR.19,98	40	ps02	8	43.31	0.06
MAR.31,98	40	ps03	8	43.06	0.03
MAR.12,98	40	ps05	8	44.78	0.05
APR.28,98	40	ps07	8	43.98	0.12
APR.02,98	60	ps02	8	43.40	0.15
APR.14,98	60	ps03	8	44.41	0.10
MAR.26,98	60	ps05	8	43.17	0.02
APR.07,98	60	ps07	8	43.77	0.09

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	No. of Air Filtration System Flow Obs	Mean Air Filtration System Flow (L/min)	S.E. of the Mean Air Filt. System Flow
FEB.12,98	0	ps02	8	1021.02	18.18
FEB.16,98	0	ps03	9	995.10	22.87
FEB.18,98	0	ps05	9	999.95	8.27
MAR.17,98	0	ps07	8	932.38	2.82
MAR.03,98	20	ps02	8	923.54	12.96
MAR.10,98	20	ps03	7	318.32	30.16
FEB.26,98	20	ps05	8	847.15	42.85
MAR.24,98	20	ps07	7	672.37	37.75
MAR.19,98	40	ps02	8	517.82	34.14
MAR.31,98	40	ps03	7	662.96	16.86
MAR.12,98	40	ps05	5	230.97	69.58
APR.28,98	40	ps07	8	456.84	53.75
APR.02,98	60	ps02	7	298.21	23.43
APR.14,98	60	ps03	6	656.59	36.40
MAR.26,98	60	ps05	8	762.67	5.31
APR.07,98	60	ps07	6	438.71	73.83

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	Number of Mixed Inlet Flow Obs.	Mean Mixed Inlet Flow (L/min)	S.E. of Mean Mixed Inlet Flow
FEB.12,98	0	ps02	7	792.45	91.07
FEB.16,98	0	ps03	9	925.52	3.62
FEB.18,98	0	ps05	9	929.15	3.14
MAR.17,98	0	ps07	8	887.58	1.47
MAR.03,98	20	ps02	8	911.45	2.01
MAR.10,98	20	ps03	7	948.22	6.29
FEB.26,98	20	ps05	8	931.88	1.76
MAR.24,98	20	ps07	7	922.96	3.25
MAR.19,98	40	ps02	8	901.08	6.67
MAR.31,98	40	ps03	7	908.87	2.88
MAR.12,98	40	ps05	5	956.72	8.54
APR.28,98	40	ps07	8	955.81	1.99
APR.02,98	60	ps02	8	939.68	8.26
APR.14,98	60	ps03	6	929.15	3.95
MAR.26,98	60	ps05	8	947.87	3.33
APR.07,98	60	ps07	8	963.34	9.55

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	No. of Stage 1 Major Pressure Obs.	Mean Stage 1 Major Pressure (in.w.g.)	S.E. of the Mean Stage 1 Major Pressure
FEB.12,98	0	ps02	8	113.13	0.63
FEB.16,98	0	ps03	9	113.33	0.26
FEB.18,98	0	ps05	9	115.11	0.51
MAR.17,98	0	ps07	8	97.38	0.42
MAR.03,98	20	ps02	9	100.00	0.00
MAR.10,98	20	ps03	8	107.50	1.09
FEB.26,98	20	ps05	8	114.38	0.18
MAR.24,98	20	ps07	8	106.00	1.00
MAR.19,98	40	ps02	8	103.81	1.59
MAR.31,98	40	ps03	8	105.00	0.00
MAR.12,98	40	ps05	8	120.19	2.15
APR.28,98	40	ps07	8	113.81	0.57
APR.02,98	60	ps02	8	110.63	4.12
APR.14,98	60	ps03	8	112.50	0.38
MAR.26,98	60	ps05	8	112.69	0.25
APR.07,98	60	ps07	8	119.38	2.27

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	No. of Stage 2 Major Pressure Obs.	Mean Stage 2 Major Pressure (in.w.g.)	S.E. of the Mean Stage 2 Major Pressure
FEB.12,98	0	ps02	8	114.38	0.63
FEB.16,98	0	ps03	9	115.00	0.00
FEB.18,98	0	ps05	9	114.89	0.20
MAR.17,98	0	ps07	8	100.50	1.66
MAR.03,98	20	ps02	9	100.00	0.00
MAR.10,98	20	ps03	8	111.31	1.07
FEB.26,98	20	ps05	8	116.00	0.71
MAR.24,98	20	ps07	8	120.38	0.73
MAR.19,98	40	ps02	8	105.81	1.22
MAR.31,98	40	ps03	8	113.19	0.19
MAR.12,98	40	ps05	8	116.00	1.16
APR.28,98	40	ps07	8	115.94	3.39
APR.02,98	60	ps02	8	115.63	2.30
APR.14,98	60	ps03	8	112.13	0.44
MAR.26,98	60	ps05	8	112.75	0.25
APR.07,98	60	ps07	8	122.31	0.77

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	No. of Stage 1 Minor Pressure Obs.	Mean Stage 1 Minor Pressure (in.w.g.)	S.E. of the Mean Stage 1 Minor Pressure
FEB.12,98	0	ps02	8	3.00	0.00
FEB.16,98	0	ps03	9	2.72	0.09
FEB.18,98	0	ps05	9	3.11	0.11
MAR.17,98	0	ps07	8	2.28	0.02
MAR.03,98	20	ps02	9	2.37	0.03
MAR.10,98	20	ps03	8	2.50	0.00
FEB.26,98	20	ps05	8	2.50	0.00
MAR.24,98	20	ps07	8	2.50	0.00
MAR.19,98	40	ps02	8	2.50	0.00
MAR.31,98	40	ps03	8	2.50	0.00
MAR.12,98	40	ps05	8	2.50	0.00
APR.28,98	40	ps07	8	2.50	0.00
APR.02,98	60	ps02	8	2.50	0.00
APR.14,98	60	ps03	8	2.50	0.00
MAR.26,98	60	ps05	8	2.50	0.00
APR.07,98	60	ps07	8	2.50	0.00

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	No. of Stage 2 Minor Pressure Obs.	Mean Stage 2 Minor Pressure (in.w.g.)	S.E. of the Mean Stage 2 Minor Pressure
FEB.12,98	0	ps02	8	5.06	0.06
FEB.16,98	0	ps03	9	5.00	0.00
FEB.18,98	0	ps05	9	5.31	0.05
MAR.17,98	0	ps07	8	4.90	0.02
MAR.03,98	20	ps02	9	5.50	0.00
MAR.10,98	20	ps03	8	5.00	0.00
FEB.26,98	20	ps05	8	5.50	0.00
MAR.24,98	20	ps07	8	5.16	0.04
MAR.19,98	40	ps02	8	5.20	0.02
MAR.31,98	40	ps03	8	5.40	0.05
MAR.12,98	40	ps05	8	5.39	0.06
APR.28,98	40	ps07	8	5.15	0.08
APR.02,98	60	ps02	8	5.10	0.07
APR.14,98	60	ps03	8	5.13	0.03
MAR.26,98	60	ps05	8	5.20	0.00
APR.07,98	60	ps07	8	5.36	0.05

Table A1-4 (continued). Summary Data for Human Exposure Facility Variables

Date	Target Exposure (ug/m3)	Subject ID	Number of Mixed Inlet Diff. Press. Obs.	Mean Mixed Inlet Diff. Press. (in.w.g.)	S.E. of the Mean Dilution Inlet Flow
FEB.12,98	0	ps02	8	-0.03	0.00
FEB.16,98	0	ps03	9	-0.04	0.00
FEB.18,98	0	ps05	9	-0.05	0.00
MAR.17,98	0	ps07	8	-0.03	0.00
MAR.03,98	20	ps02	8	-0.04	0.00
MAR.10,98	20	ps03	7	-0.02	0.00
FEB.26,98	20	ps05	8	-0.03	0.00
MAR.24,98	20	ps07	8	-0.01	0.00
MAR.19,98	40	ps02	8	-0.11	0.00
MAR.31,98	40	ps03	7	-0.20	0.02
MAR.12,98	40	ps05	5	-0.02	0.01
APR.28,98	40	ps07	8	-0.05	0.02
APR.02,98	60	ps02	7	-0.02	0.00
APR.14,98	60	ps03	6	-0.08	0.01
MAR.26,98	60	ps05	8	-0.29	0.00
APR.07,98	60	ps07	6	-0.01	0.00

Table A1-5. Environment Canada Data

Month	Day	Year	Time	Target PM2.5 Exposure Conc. (ug/m3)	Subject ID	Outside Temperature (Celsius)	Barometric Pressure (kPa)	Outside Relative Humidity (%)	Wind Speed (km/h)
2	12	98	.	0	ps02	.	.	.	.
2	16	98	.	0	ps03	.	.	.	.
2	18	98	915	0	ps05	1.4	100.25	94	29.5
2	18	98	1300	0	ps05	2.2	100.18	94	24.1
3	17	98	900	0	ps07	0.2	103.37	70	16.6
3	17	98	1300	0	ps07	3.5	103.02	55	22.3
3	3	98	900	20	ps02	2.5	100.12	84	9.4
3	3	98	1221	20	ps02	3.7	100.15	76	11.2
3	3	98	1428	20	ps02	3.7	100.14	76	11.2
3	10	98	900	20	ps03	-8.2	101.23	62	40.7
3	10	98	1200	20	ps03	-6.4	101.57	60	31.7
3	10	98	1300	20	ps03	-5.8	101.63	61	37.1
2	26	98	900	20	ps05	0.6	102.12	82	7.6
2	26	98	1000	20	ps05	2.3	102.12	75	5.4
2	26	98	1300	20	ps05	7.2	102.01	47	9.4
2	26	98	1600	20	ps05	8.6	101.84	44	7.6
3	24	98	900	20	ps07	-0.6	102.32	57	9.4

Table A1-5 (continued). Environment Canada Data

Month	Day	Year	Time	Target PM2.5 Exposure Conc. (ug/m3)	Subject ID	Outside Temperature (Celsius)	Barometric Pressure (kPa)	Outside Relative Humidity (%)	Wind Speed (km/h)
3	24	98	1000	20	ps07	1.3	102.36	57	18.4
3	24	98	1500	20	ps07	3.8	102.53	37	11.2
3	19	98	900	40	ps02	1.3	101.24	90	14.8
3	19	98	1300	40	ps02	1.3	101.07	90	13.0
3	19	98	1410	40	ps02	1.4	101.04	89	16.6
3	31	98	800	40	ps03	18.3	100.54	65	14.8
3	31	98	900	40	ps03	22.1	100.52	54	25.9
3	31	98	1000	40	ps03	23.5	100.51	53	29.5
3	31	98	1100	40	ps03	24.1	100.53	50	37.1
3	31	98	1300	40	ps03	24.7	100.54	49	35.3
3	12	98	800	40	ps05	-10.4	102.61	57	22.3
3	12	98	1100	40	ps05	-6.6	102.67	46	42.5
3	12	98	1200	40	ps05	-6.3	102.67	48	38.9
4	28	98	900	40	ps07	8.0	103.10	48	5.4
4	28	98	1000	40	ps07	9.6	103.09	42	7.6
4	28	98	1100	40	ps07	10.4	103.08	38	7.6
4	28	98	1200	40	ps07	11.6	103.04	41	7.6

Table A1-5 (continued). Environment Canada Data

Month	Day	Year	Time	Target PM2.5 Exposure Conc. (ug/m3)	Subject ID	Outside Temperature (Celsius)	Barometric Pressure (kPa)	Outside Relative Humidity (%)	Wind Speed (km/h)
4	28	98	1400	40	ps07	14.6	102.90	34	16.6
4	28	98	1500	40	ps07	15.6	102.84	29	14.8
4	28	98	1600	40	ps07	16.2	102.71	27	20.5
4	2	98	600	60	ps02	5.9	100.44	90	7.6
4	2	98	700	60	ps02	5.8	100.50	88	11.2
4	2	98	800	60	ps02	6.4	100.53	84	16.6
4	2	98	1000	60	ps02	7.6	100.63	77	27.7
4	14	98	900	60	ps03	11.4	100.86	53	11.2
4	14	98	1000	60	ps03	13.0	100.80	50	9.4
4	14	98	1100	60	ps03	14.4	100.77	46	13.0
4	14	98	1200	60	ps03	16.0	100.72	45	16.6
4	14	98	1300	60	ps03	15.3	100.69	43	20.5
3	26	98	800	60	ps05	8.7	101.61	75	13.0
3	26	98	900	60	ps05	10.0	101.56	73	16.6
3	26	98	1000	60	ps05	11.3	101.52	70	22.3
3	26	98	1200	60	ps05	14.0	101.43	67	25.9
3	26	98	1600	60	ps05	19.0	101.18	63	27.7

Table A1-5 (continued). Environment Canada Data

Month	Day	Year	Time	Target PM2.5 Exposure Conc. (ug/m3)	Subject ID	Outside Temperature (Celsius)	Barometric Pressure (kPa)	Outside Relative Humidity (%)	Wind Speed (km/h)
4	7	98	900	60	ps07	5.0	101.63	41	5.4
4	7	98	1100	60	ps07	9.8	101.63	33	0.0
4	7	98	1300	60	ps07	11.5	101.51	33	14.8

Appendix Two. Data for Chapter Four

Table A2-1. Summary Diffusing Capacity for CO Data

Subject ID	Target Exposure (ug/m3)	Date	Percentage Change in VC	Percentage Change in DLCO	Percentage Change in SB-TLC
ps02	0	FEB.12,98	-1.63	15.58	-1.64
ps02	20	MAR.03,98	2.69	7.08	1.49
ps02	40	MAR.19,98	10.89	-1.41	-0.32
ps02	60	APR.02,98	0.20	-3.75	0.81
ps03	0	FEB.16,98	-3.57	-21.46	-0.45
ps03	20	MAR.10,98	-0.63	-1.06	-1.89
ps03	40	MAR.31,98	1.18	-4.77	-0.83
ps03	60	APR.14,98	1.71	-0.98	-0.20
ps05	0	FEB.18,98	-1.14	-3.32	1.15
ps05	20	FEB.26,98	-1.68	-4.35	-2.87
ps05	40	MAR.12,98	-5.81	-15.10	-4.37
ps05	60	MAR.26,98	0.75	-2.23	0.72
ps07	0	MAR.17,98	1.24	-14.73	1.60
ps07	20	MAR.24,98	0.36	-2.18	0.30
ps07	40	APR.28,98	-0.36	-4.51	-0.74
ps07	60	APR.07,98	-0.56	-8.83	-0.76

Table A2-2. Summary Body Plethysmography Data

Subject ID	Target Exposure (ug/m3)	Date	Percentage Change in TGV	Percentage Change in Raw	Percentage Change in SRaw
ps02	0	FEB.12,98	7.93	9.90	1.83
ps02	20	MAR.03,98	-3.67	-4.38	-0.74
ps02	40	MAR.19,98	-2.94	9.66	12.98
ps02	60	APR.02,98	-7.23	-8.73	-1.62
ps03	0	FEB.16,98	5.78	3.73	-1.94
ps03	20	MAR.10,98	-1.26	2.76	4.07
ps03	40	MAR.31,98	-0.84	0.91	1.76
ps03	60	APR.14,98	-4.20	8.29	13.04
ps05	0	FEB.18,98	6.19	7.69	1.42
ps05	20	FEB.26,98	-2.60	-3.57	-1.00
ps05	40	MAR.12,98	-0.32	7.93	8.27
ps05	60	MAR.26,98	-10.59	0.68	12.60
ps07	0	MAR.17,98	2.65	7.10	4.33
ps07	20	MAR.24,98	-0.72	4.00	4.75
ps07	40	APR.28,98	11.76	-10.00	-19.47
ps07	60	APR.07,98	-3.51	0.00	3.64

Table A2-2 (continued). Summary Body Plethysmography Data

Subject ID	Target Exposure (ug/m3)	Date	Percentage Change in IC	Percentage Change in TLC	Percentage Change in RV
ps02	0	FEB.12,98	0.00	3.03	21.69
ps02	20	MAR.03,98	10.98	4.91	15.19
ps02	40	MAR.19,98	6.84	5.43	38.24
ps02	60	APR.02,98	2.29	-1.40	-9.57
ps03	0	FEB.16,98	0.00	2.84	11.93
ps03	20	MAR.10,98	6.55	2.56	22.33
ps03	40	MAR.31,98	8.37	3.77	4.13
ps03	60	APR.14,98	-0.81	-2.47	-2.68
ps05	0	FEB.18,98	-6.70	-1.18	-1.54
ps05	20	FEB.26,98	-1.52	-1.99	-1.44
ps05	40	MAR.12,98	1.89	-3.89	-15.92
ps05	60	MAR.26,98	8.31	-0.86	-3.62
ps07	0	MAR.17,98	9.23	2.06	1.67
ps07	20	MAR.24,98	0.25	-1.33	-25.00
ps07	40	APR.28,98	-0.48	5.04	34.71
ps07	60	APR.07,98	-2.54	-2.95	-11.80

Table A2-3. Summary Spirometry Data

Subject ID	Target Exposure (ug/m3)	Date	Percentage Change in FVC	Percentage Change in FEV1	Percentage Change in FEV1/FVC Ratio	Percentage Change in PEFR
ps02	0	FEB.12,98	2.65	4.99	2.31	0.99
ps02	20	MAR.03,98	1.17	2.08	0.80	-0.75
ps02	40	MAR.19,98	1.75	5.04	3.28	5.12
ps02	60	APR.02,98	2.85	3.68	0.83	-6.77
ps03	0	FEB.16,98	-6.05	-3.61	2.61	-7.31
ps03	20	MAR.10,98	-0.86	0.90	1.79	2.90
ps03	40	MAR.31,98	4.02	4.56	0.53	4.35
ps03	60	APR.14,98	1.94	2.99	1.08	4.49
ps05	0	FEB.18,98	-6.59	-0.95	5.96	0.81
ps05	20	FEB.26,98	-0.78	2.30	3.16	-2.48
ps05	40	MAR.12,98	-5.01	0.81	6.11	3.51
ps05	60	MAR.26,98	-0.90	2.62	3.58	3.84
ps07	0	MAR.17,98	4.46	-2.15	-6.39	-2.93
ps07	20	MAR.24,98	1.72	1.54	-0.24	-2.42
ps07	40	APR.28,98	1.49	6.74	5.22	-4.42
ps07	60	APR.07,98	1.45	-0.38	-1.77	0.34

Table A2-3 (continued). Summary Spirometry Data

Subject ID	Target Exposure (ug/m3)	Date	Percentage Change in V50	Percentage Change in V25	Percentage Change in V25-75	Percentage Change in V75
ps02	0	FEB.12,98	.	.	9.89	.
ps02	20	MAR.03,98	16.43	6.34	9.21	-0.71
ps02	40	MAR.19,98	28.83	19.26	14.33	3.24
ps02	60	APR.02,98	8.45	11.81	5.94	-0.19
ps03	0	FEB.16,98	4.37	2.81	1.11	-2.86
ps03	20	MAR.10,98	12.56	13.98	5.20	-5.56
ps03	40	MAR.31,98	5.66	11.89	8.08	6.80
ps03	60	APR.14,98	15.08	7.08	8.19	-0.84
ps05	0	FEB.18,98	6.05	19.27	10.10	.
ps05	20	FEB.26,98	8.42	10.51	6.84	-1.34
ps05	40	MAR.12,98	24.82	21.64	14.29	4.56
ps05	60	MAR.26,98	24.28	29.82	20.07	1.65
ps07	0	MAR.17,98	10.74	-27.11	11.31	-14.71
ps07	20	MAR.24,98	-12.89	8.65	-2.70	3.79
ps07	40	APR.28,98	26.89	38.75	29.07	0.00
ps07	60	APR.07,98	-17.38	-8.70	-11.67	-5.86

Table A2-4. Summary Minute Ventilation Data

Subject ID	Target Exposure (ug/m3)	Date	Percentage Change in Ve	Percentage Change in f
ps02	0	FEB.12,98	10.00	53.85
ps02	20	MAR.03,98	-37.50	-22.73
ps02	40	MAR.19,98	-20.00	0.00
ps02	60	APR.02,98	-18.18	-5.56
ps03	0	FEB.16,98	-33.33	25.00
ps03	20	MAR.10,98	-33.33	-14.29
ps03	40	MAR.31,98	-33.33	-13.64
ps03	60	APR.14,98	0.00	0.00
ps05	0	FEB.18,98	20.00	6.67
ps05	20	FEB.26,98	11.11	0.00
ps05	40	MAR.12,98	0.00	5.88
ps05	60	MAR.26,98	0.00	0.00
ps07	0	MAR.17,98	-22.22	-10.00
ps07	20	MAR.24,98	-20.00	0.00
ps07	40	APR.28,98	22.22	18.18
ps07	60	APR.07,98	-9.09	-23.08

Table A2-5. Summary Exposure Data

Subject ID	Target Exposure (ug/m3)	Date	Mean Chamber PM2.5 Conc. (filter --ug/m3	Mean Chamber PM2.5 Conc. (DT -- ug/m3)
ps02	0	FEB.12,98	5.96	0.00
ps02	20	MAR.03,98	22.71	35.80
ps02	40	MAR.19,98	.	52.26
ps02	60	APR.02,98	89.70	94.28
ps03	0	FEB.16,98	-12.98	0.00
ps03	20	MAR.10,98	.	38.24
ps03	40	MAR.31,98	44.79	59.09
ps03	60	APR.14,98	91.61	93.17
ps05	0	FEB.18,98	-16.03	0.00
ps05	20	FEB.26,98	33.59	37.34
ps05	40	MAR.12,98	.	51.07
ps05	60	MAR.26,98	63.62	93.45
ps07	0	MAR.17,98	4.07	0.00
ps07	20	MAR.24,98	38.17	38.36
ps07	40	APR.28,98	90.08	58.49
ps07	60	APR.07,98	123.67	90.91

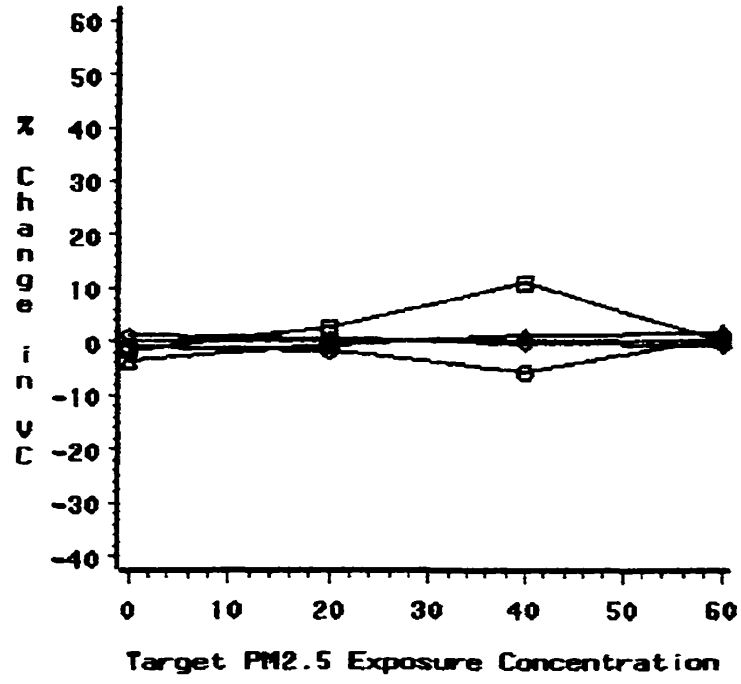
Table A2-5 (continued). Summary Exposure Data

Subject ID	Target Exposure (ug/m3)	Date	Mean Chamber CO Concentration (ppm)	Mean Chamber NO Concentration (ppb)	Mean Chamber NO2 Concentration (ppb)	Mean Chamber O3 Concentration (ppb)	Mean Chamber SO2 Concentration (ppb)
ps02	0	FEB.12,98	0.51	14.04	14.67	0.10	2.94
ps02	20	MAR.03,98	0.34	20.76	15.83	0.64	1.04
ps02	40	MAR.19,98	0.45	16.69	23.37	4.94	0.81
ps02	60	APR.02,98	0.60	27.36	21.09	6.43	0.24
ps03	0	FEB.16,98	.	.	.	.	.
ps03	20	MAR.10,98	0.07	4.99	7.35	19.55	0.45
ps03	40	MAR.31,98	0.31	9.44	15.01	4.73	1.18
ps03	60	APR.14,98	0.55	9.86	24.42	10.34	3.31
ps05	0	FEB.18,98	.	0.25	.	22.29	11.23
ps05	20	FEB.26,98	0.26	21.76	29.71	5.07	0.20
ps05	40	MAR.12,98	0.01	4.43	9.82	25.88	0.51
ps05	60	MAR.26,98	-0.23	14.56	22.16	4.10	1.91
ps07	0	MAR.17,98	0.20	13.00	20.00	5.49	2.52
ps07	20	MAR.24,98	0.22	6.17	16.52	18.40	-2.39
ps07	40	APR.28,98	0.44	36.75	27.17	6.63	7.24
ps07	60	APR.07,98	0.85	76.68	33.22	7.15	2.71

Table A2-6. Summary of Other Environmental Data

Subject ID	Target Exposure (ug/m3)	Date	Mean Chamber Relative Humidity (%)	Mean Pipe Relative Humidity (%)	Mean Chamber Air Temperature (Celsius)	Mean Pipe Temperature (Celsius)
ps02	0	FEB.12,98	45.00	.	22.25	.
ps02	20	MAR.03,98	49.45	.	21.29	.
ps02	40	MAR.19,98	46.49	11.53	21.93	16.74
ps02	60	APR.02,98	53.68	63.90	22.91	23.28
ps03	0	FEB.16,98	37.64	.	21.56	.
ps03	20	MAR.10,98	33.91	.	21.94	.
ps03	40	MAR.31,98	48.96	29.44	23.40	24.80
ps03	60	APR.14,98	38.83	16.65	24.69	24.91
ps05	0	FEB.18,98	44.52	.	22.67	.
ps05	20	FEB.26,98	39.30	.	23.19	.
ps05	40	MAR.12,98	32.03	3.19	23.20	21.73
ps05	60	MAR.26,98	39.14	20.70	23.71	21.54
ps07	0	MAR.17,98	36.56	10.46	21.29	23.65
ps07	20	MAR.24,98	37.50	9.19	23.43	23.08
ps07	40	APR.28,98	45.86	11.49	22.68	24.88
ps07	60	APR.07,98	43.44	9.63	22.69	24.87

Figure A2-1 to FigureA2-19. Percentage Change in Pulmonary Function Variables across Target Exposure $PM_{2.5}$ Concentration ($\mu g/m^3$)



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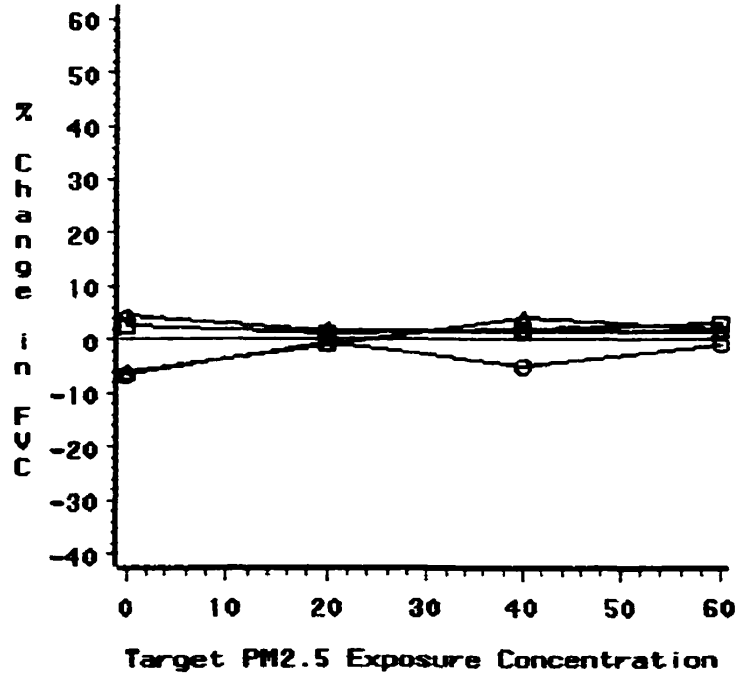

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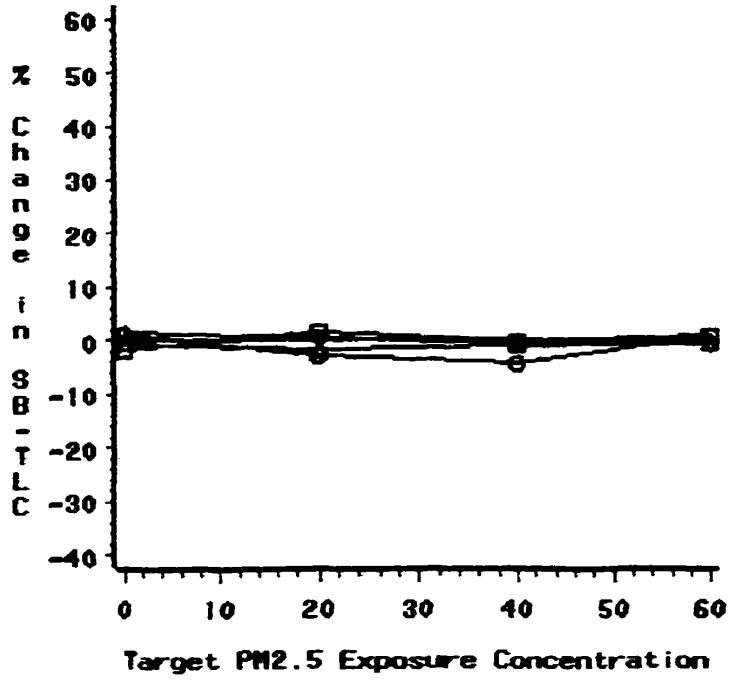

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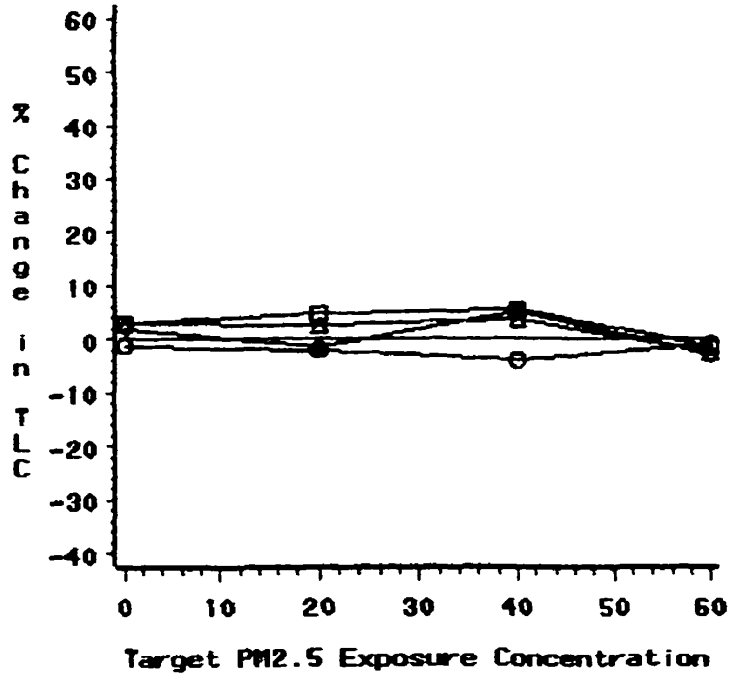

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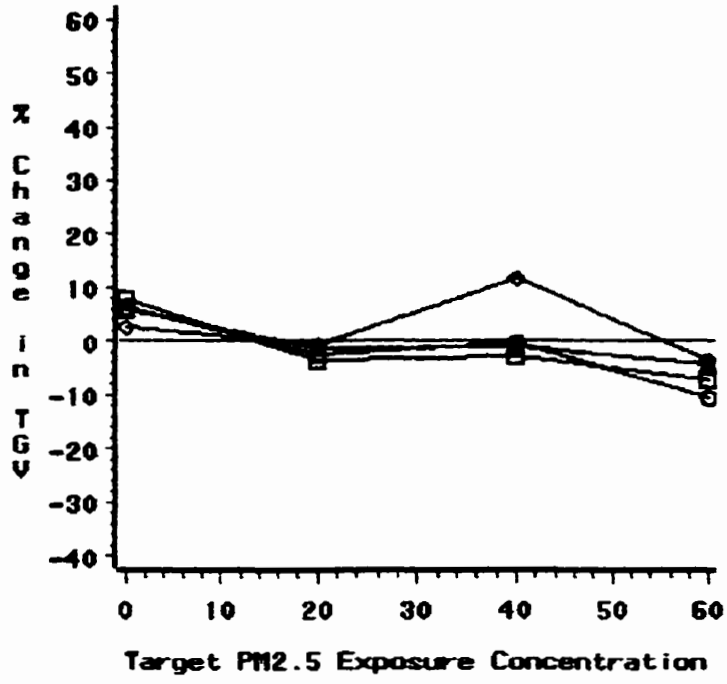

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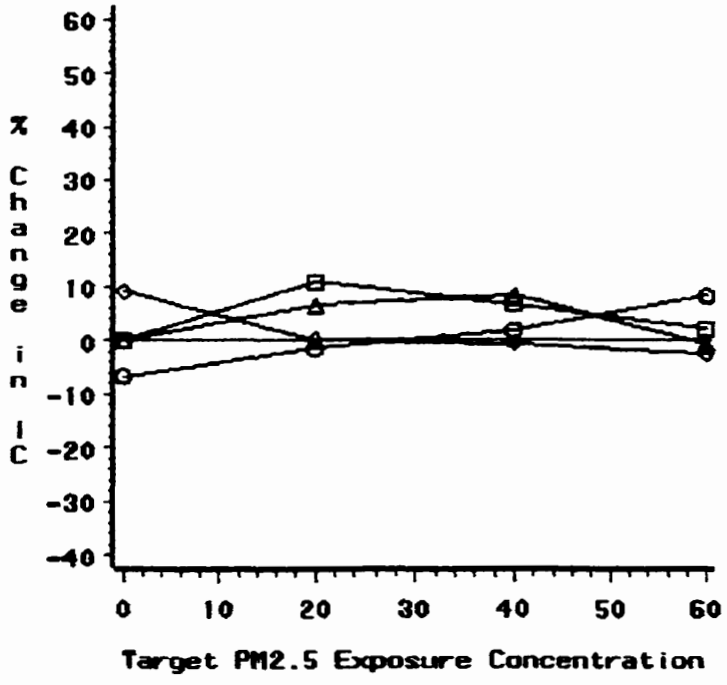

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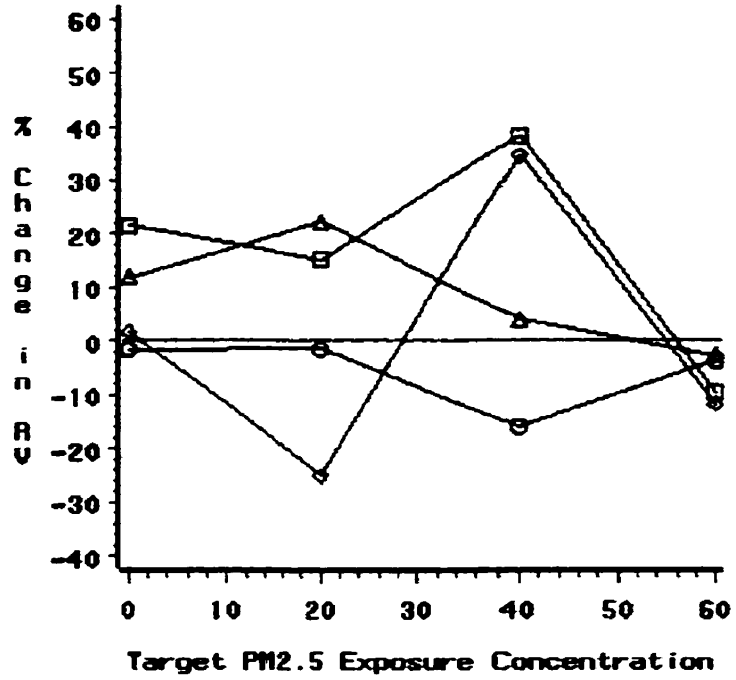
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40
30
20
10
0
-10
-20
-30
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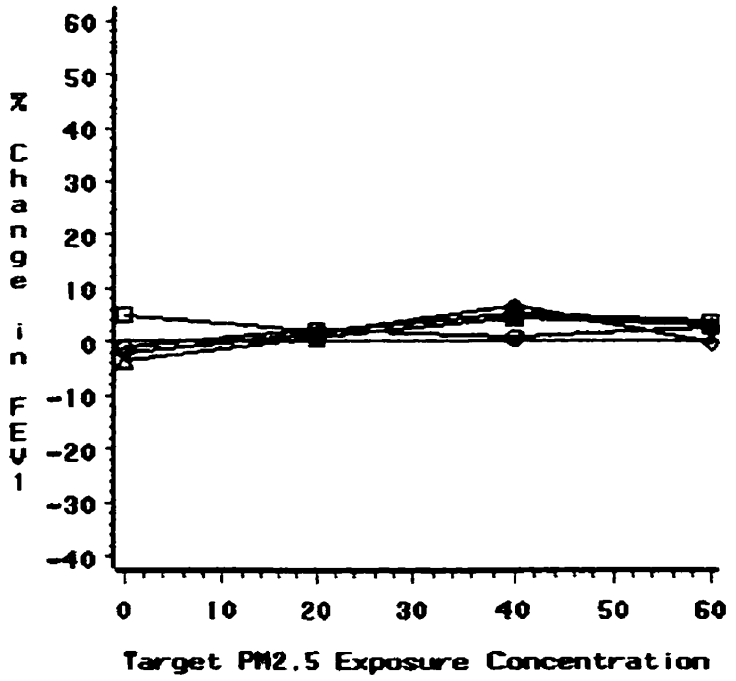
30
40
50
60
Target PM2.5 Exposure Concentration
Subject ID
ps02
ps03
ps05
ps07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Target PM2.5 Exposure Concentration
Subject ID
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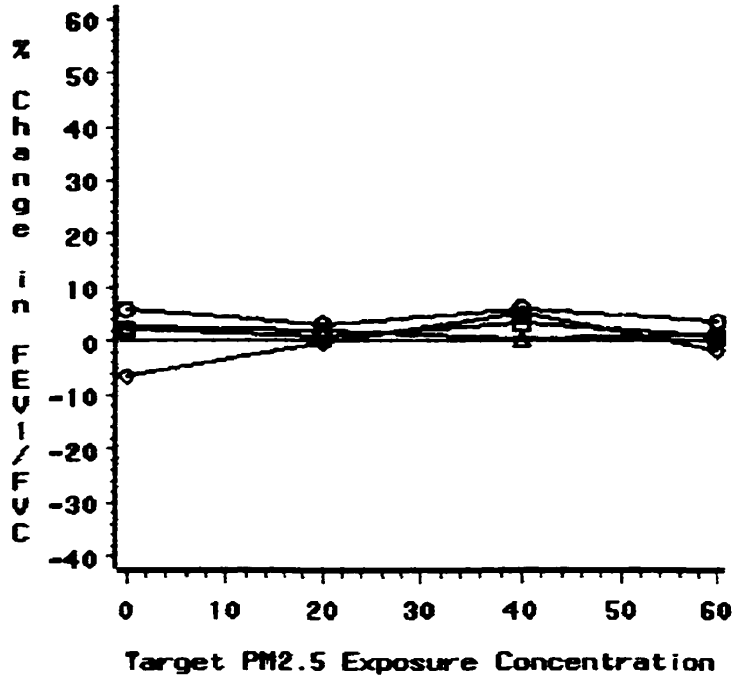

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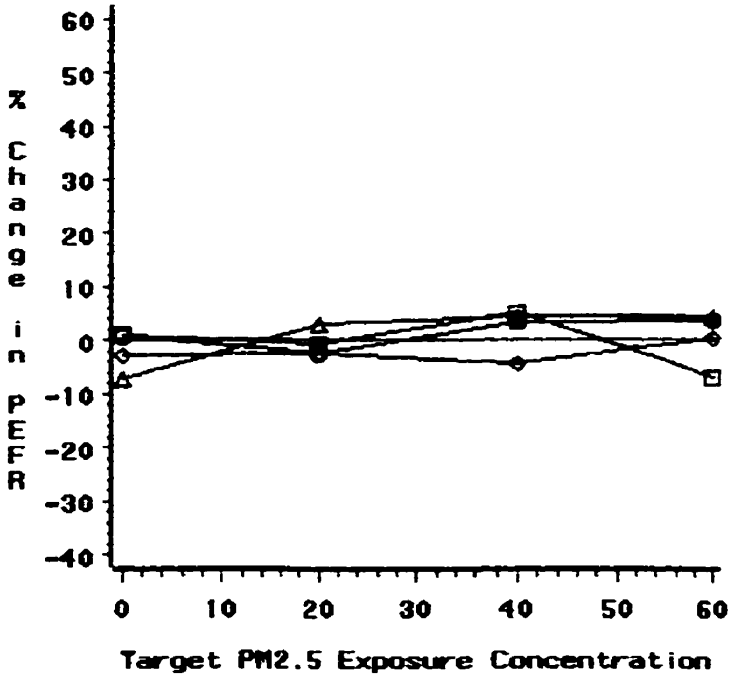

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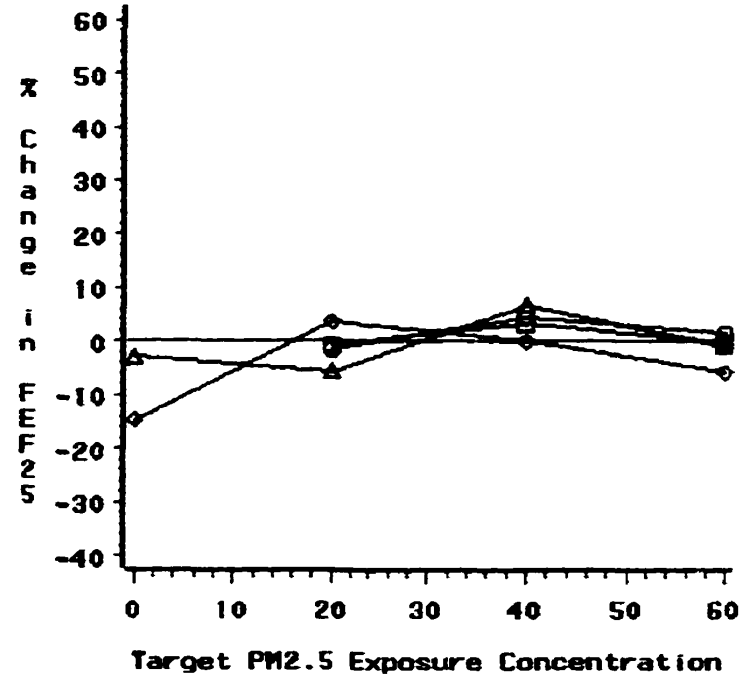
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Subject ID
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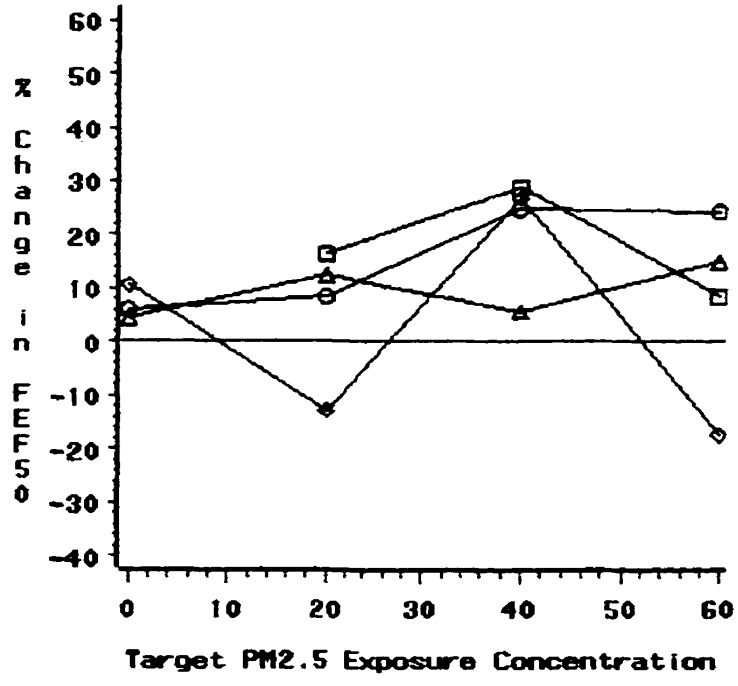
ps03
ps05
ps07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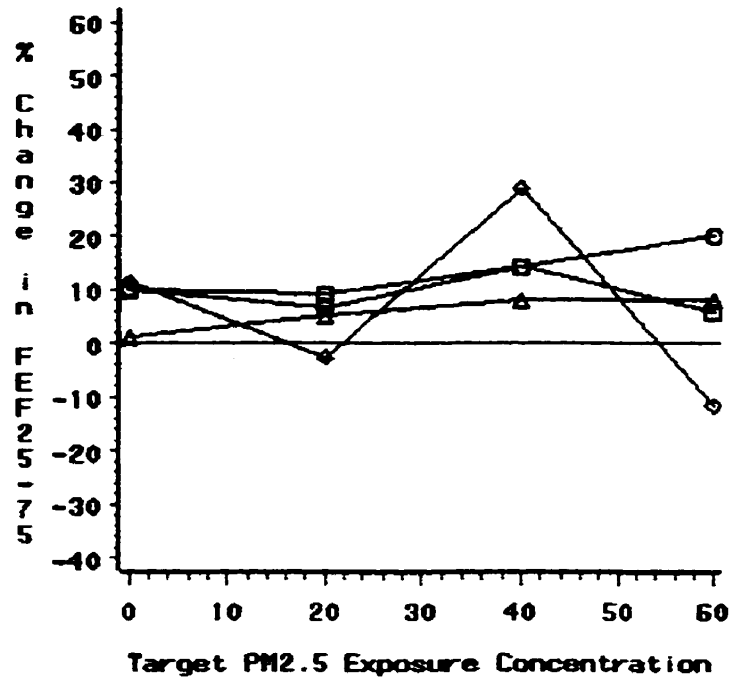
Subject ID
ps02
ps03
ps05
ps07



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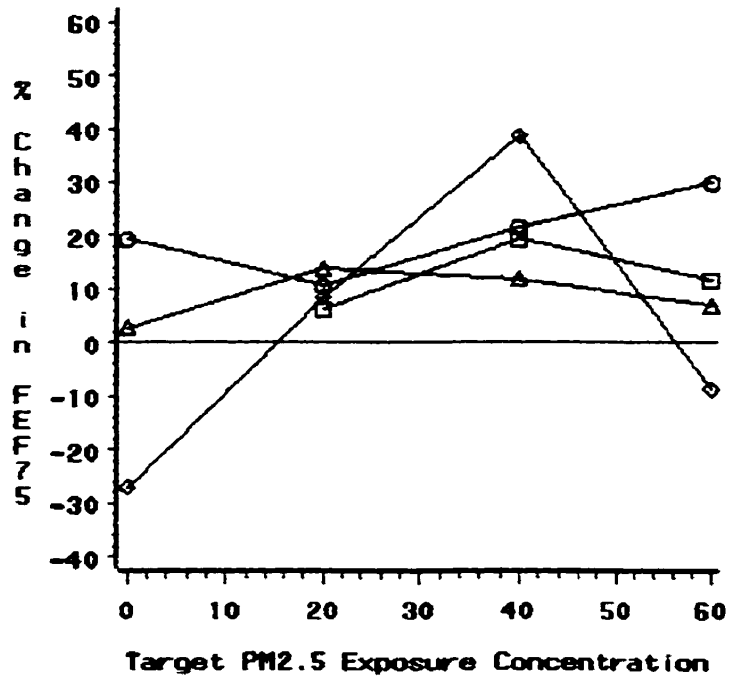

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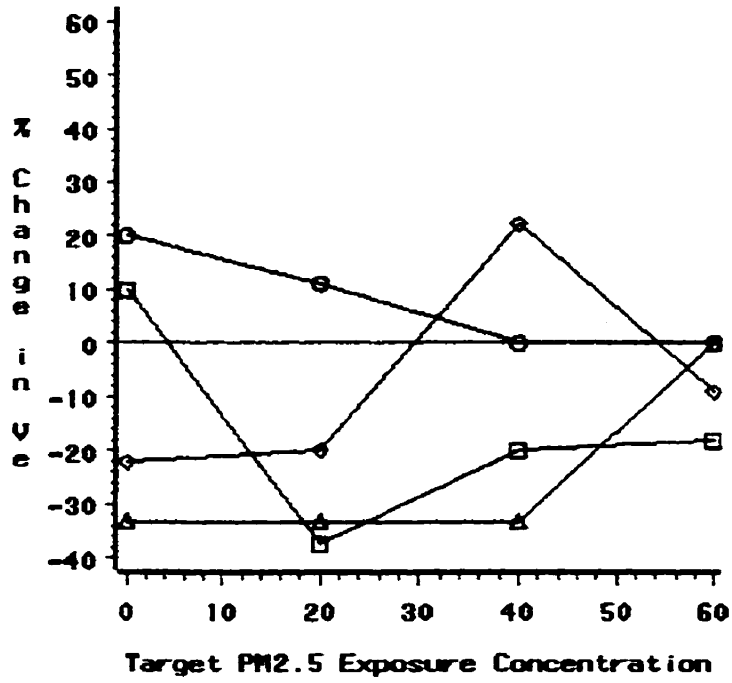
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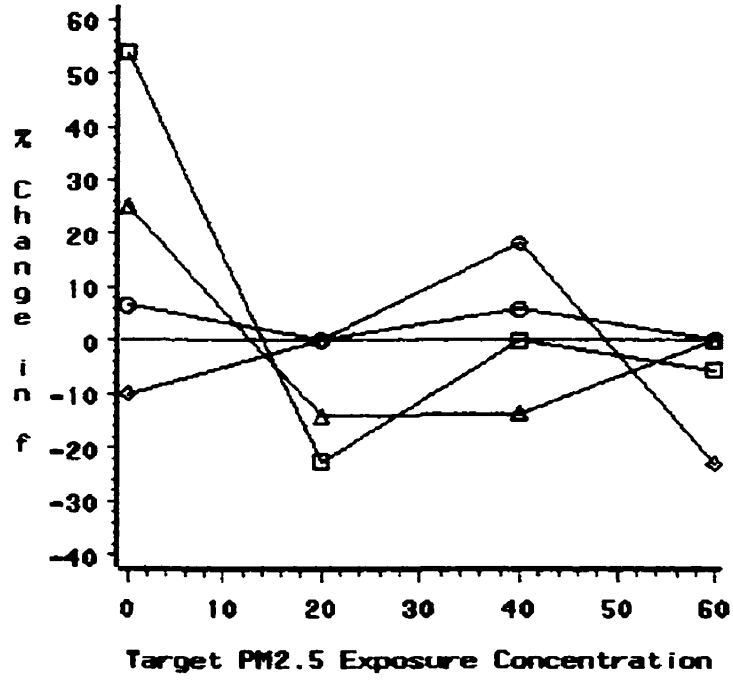
10
20
30
40
50
60
Target PM2.5 Exposure Concentration
Subject ID
ps02
ps03
ps05
ps07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% Change in Vf
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20
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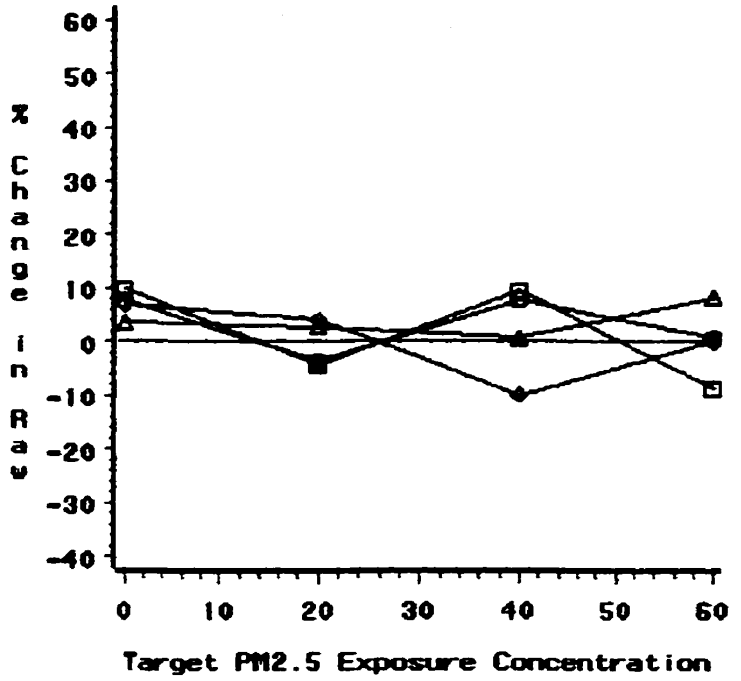
50
60
Target PM2.5 Exposure Concentration
Subject ID
ps02
ps03
ps05
ps07



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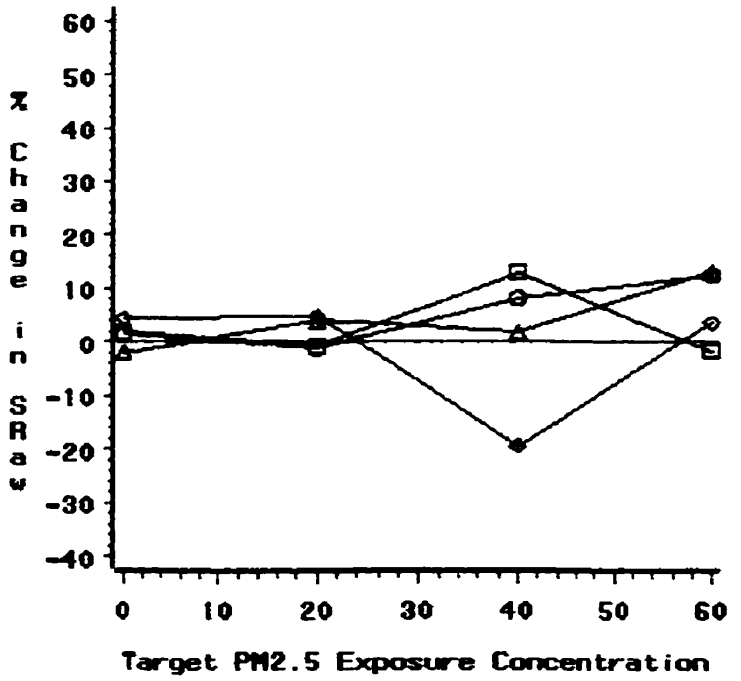

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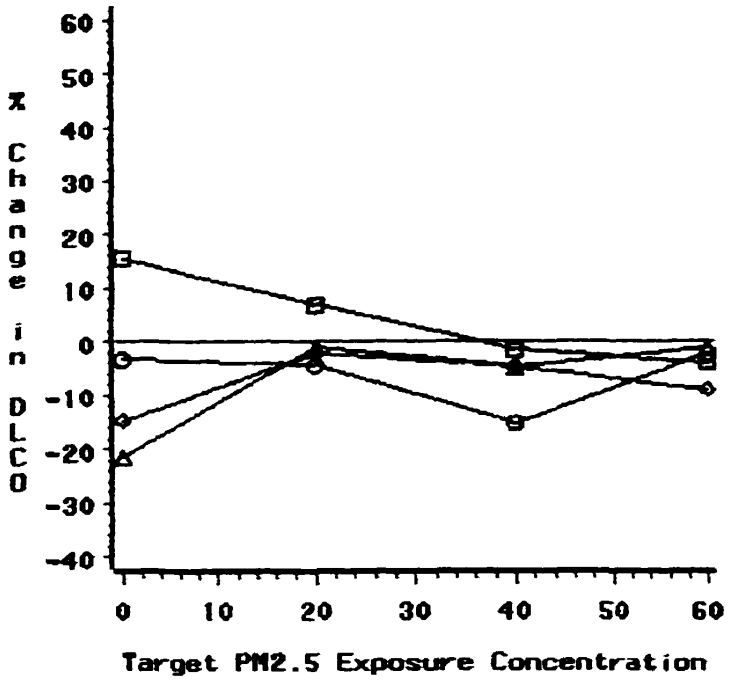

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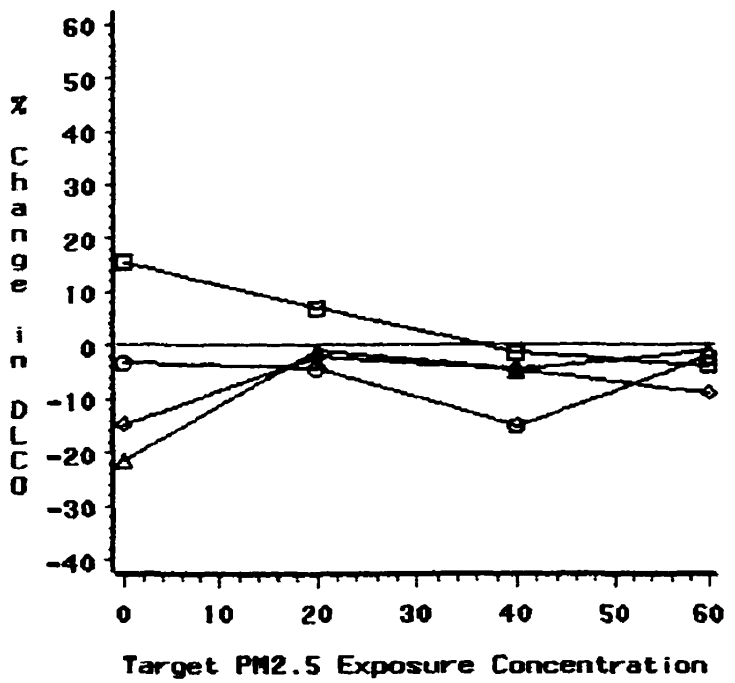

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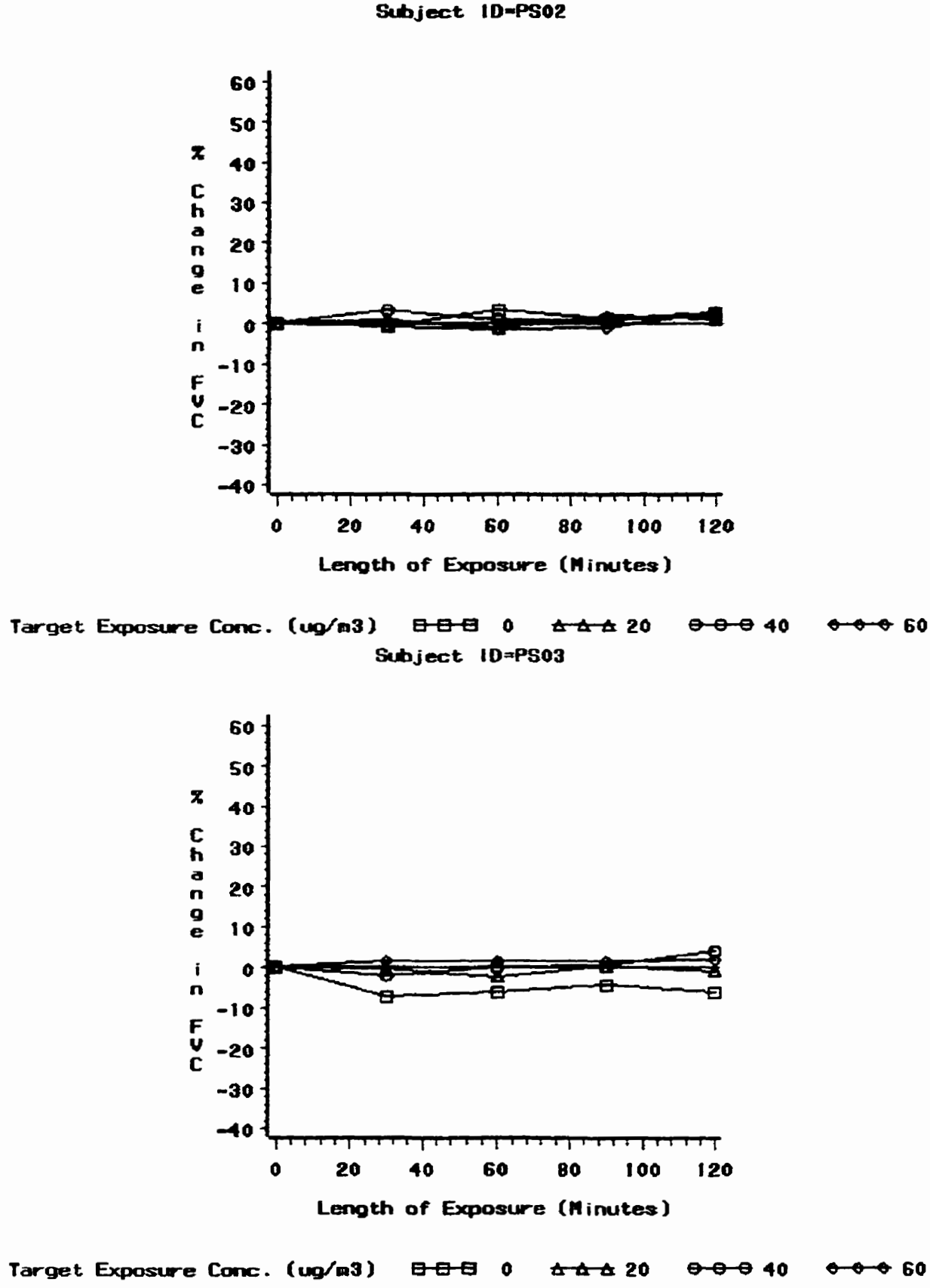
Figure A2-21 to A2-60. Percentage Change in Pulmonary Function Variables across Time



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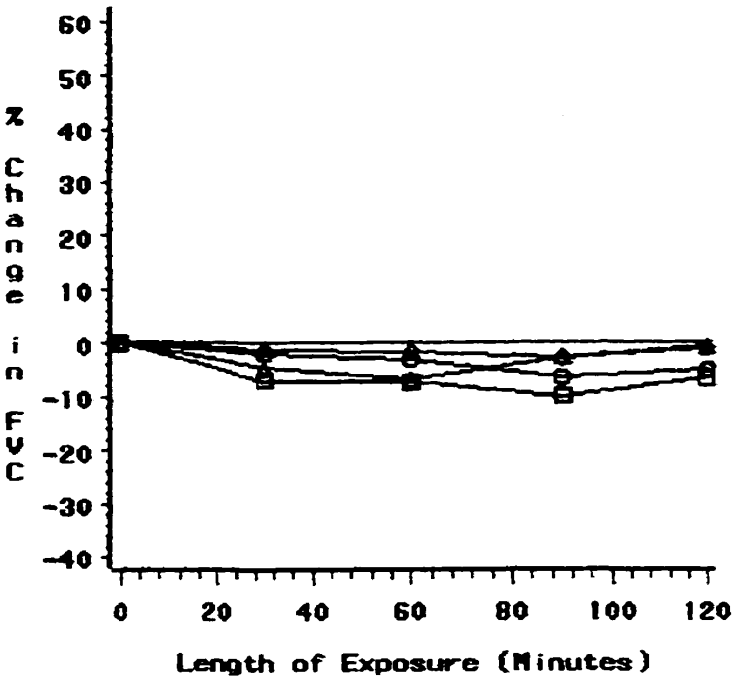

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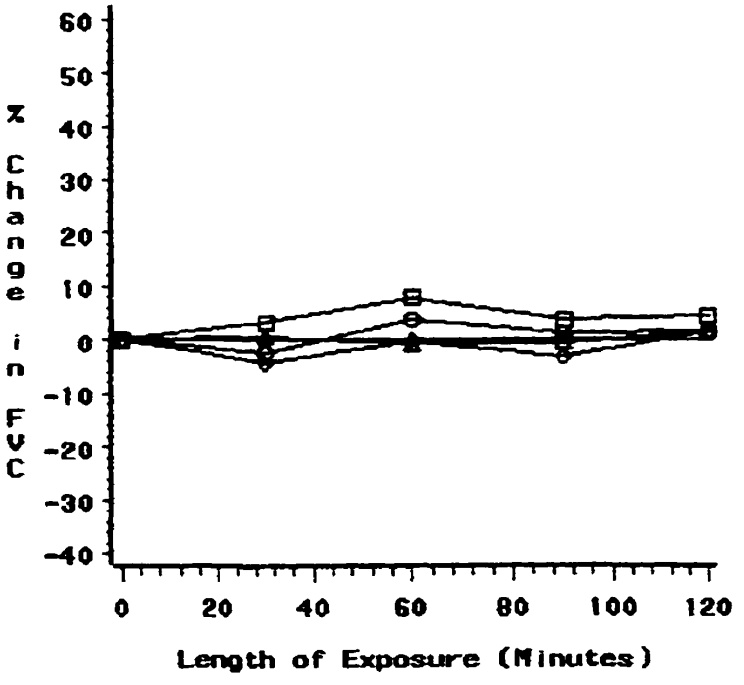

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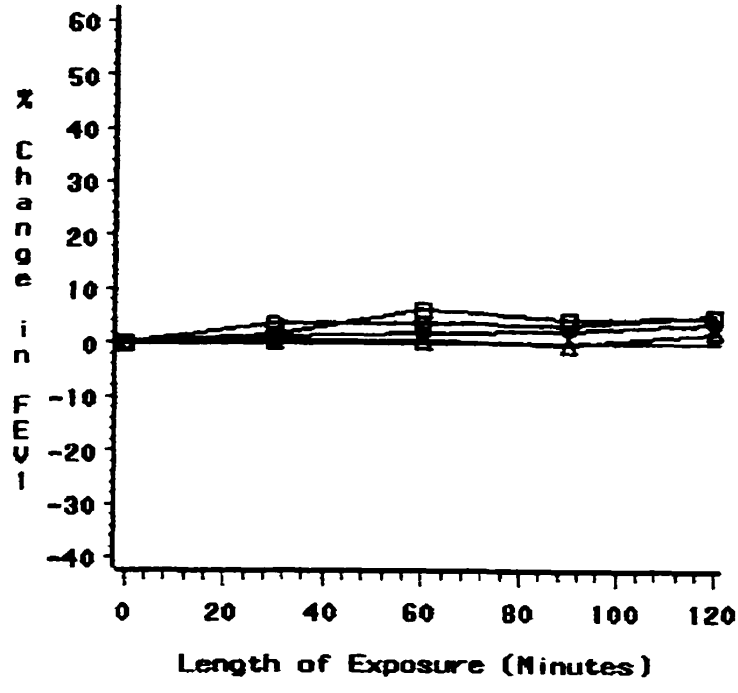

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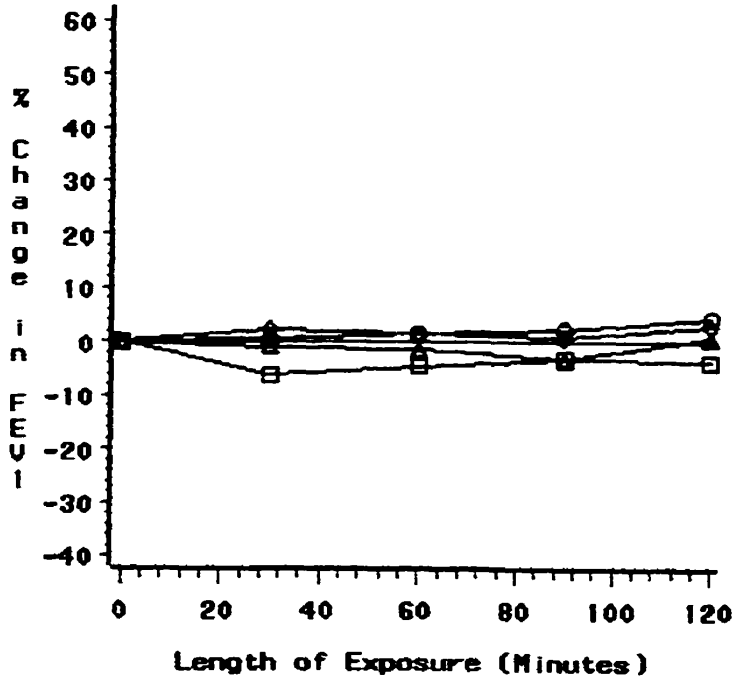

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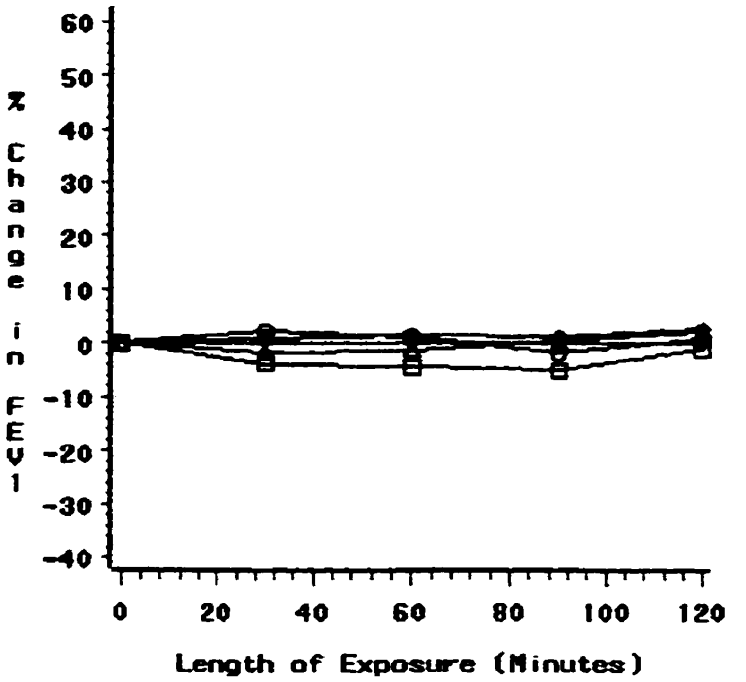

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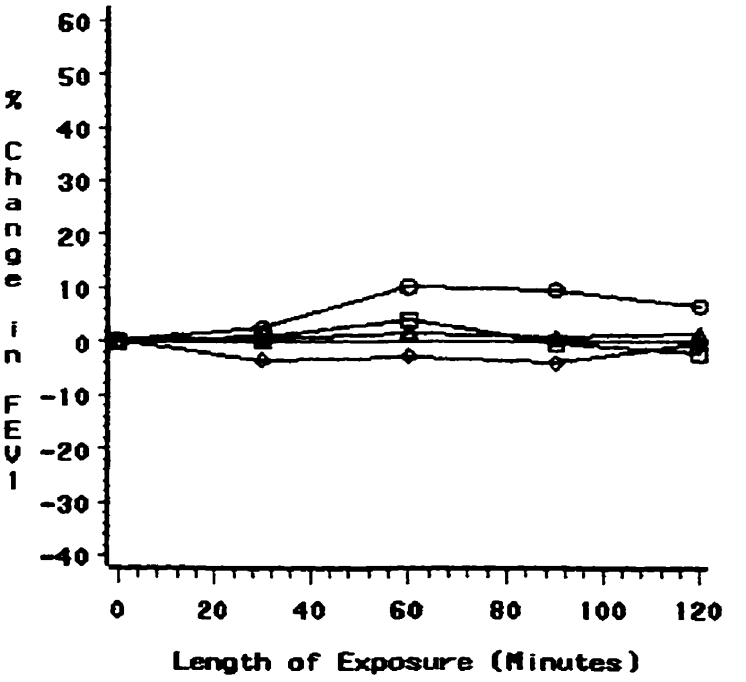

Target Exposure Conc. (ug/m3) 0 20 40 60

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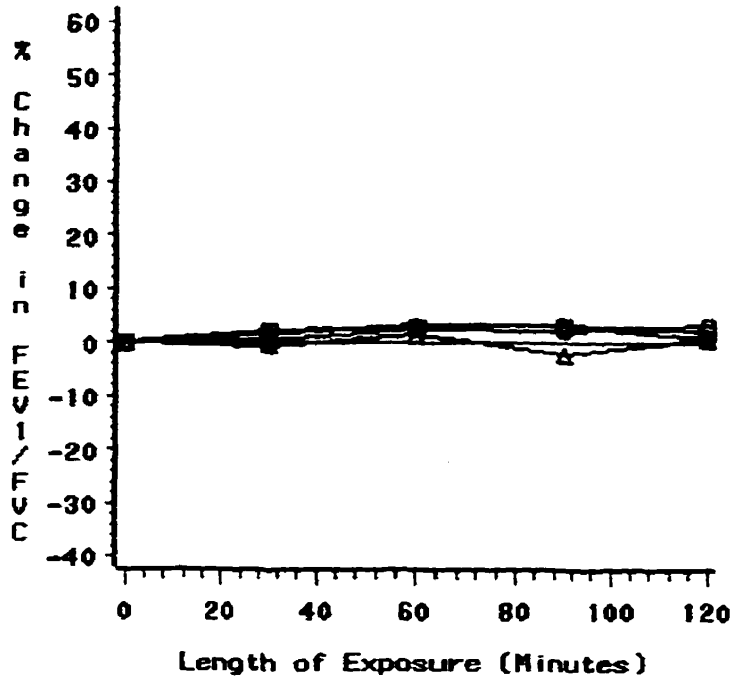

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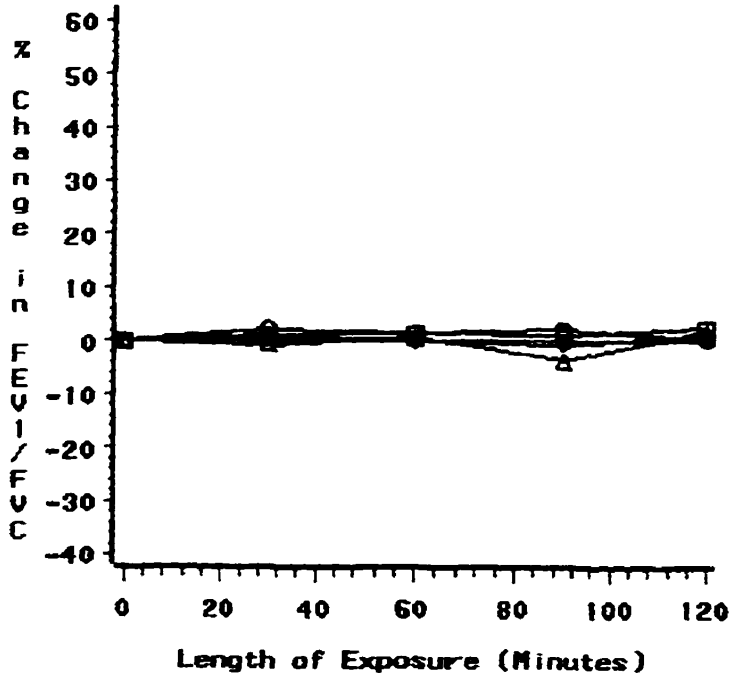

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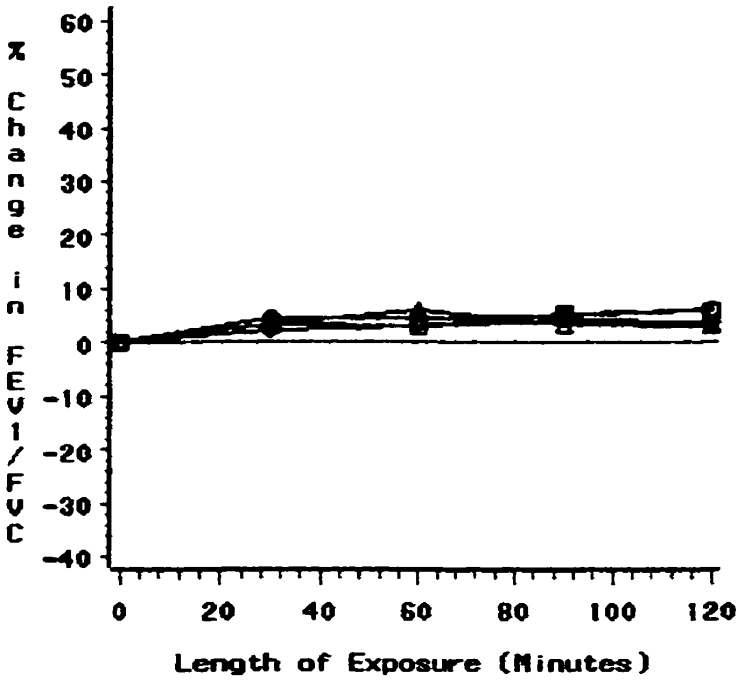

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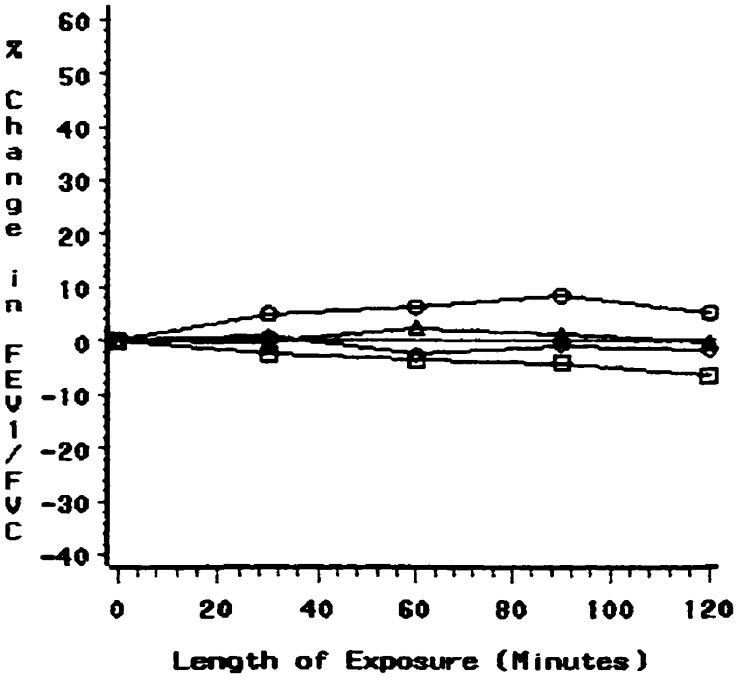

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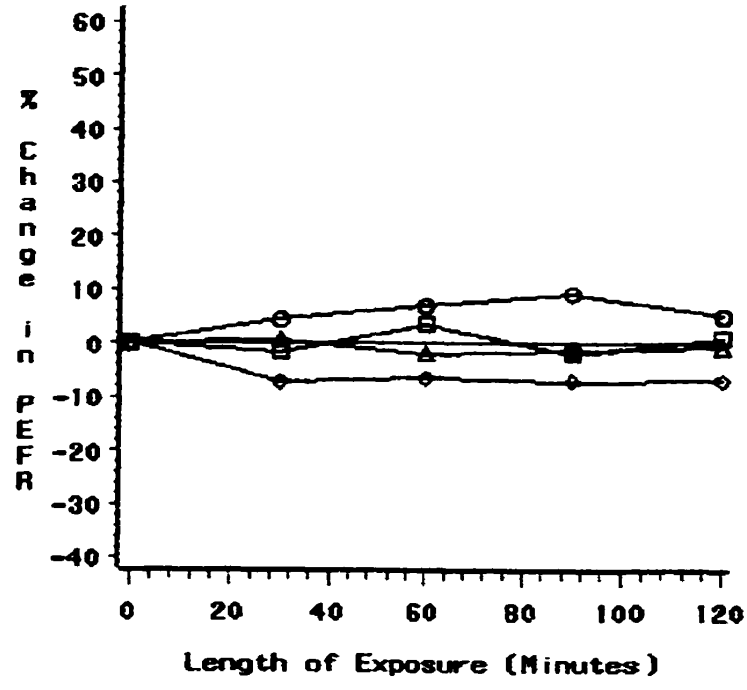

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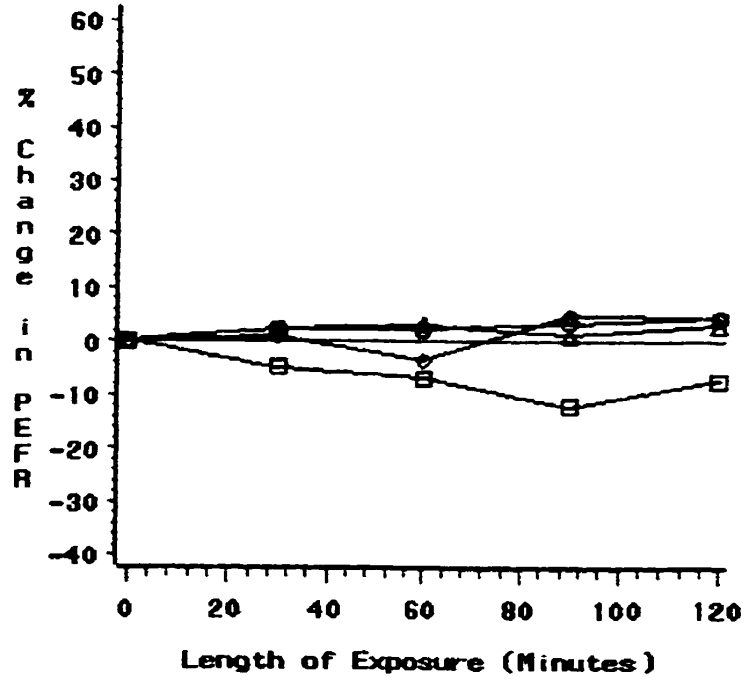

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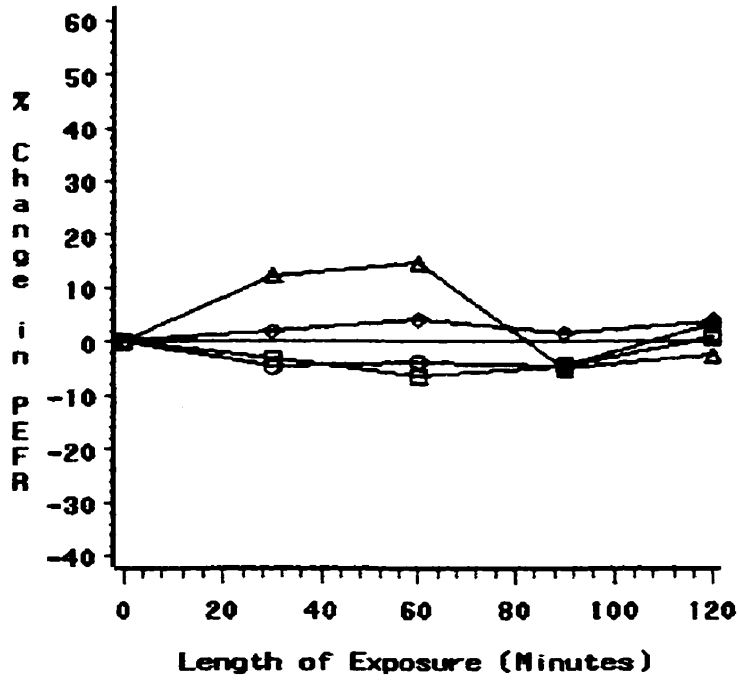

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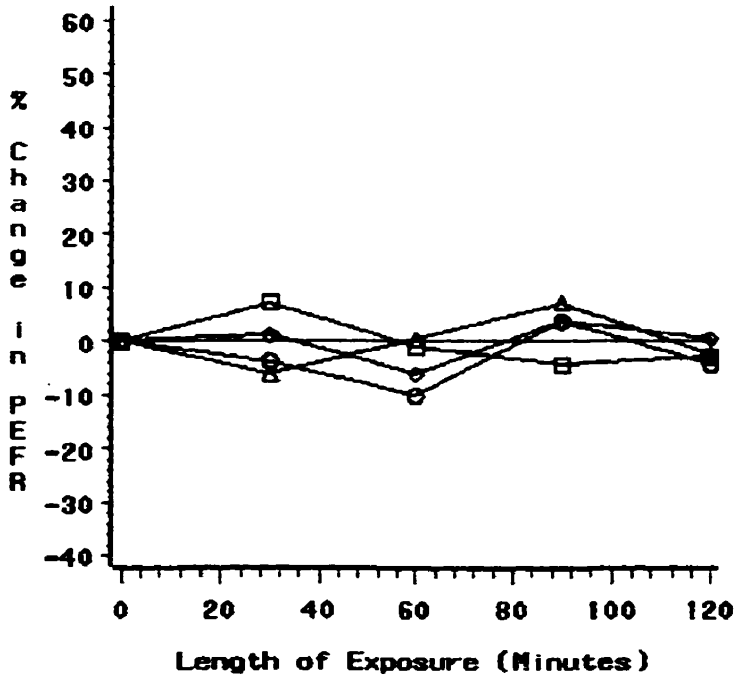

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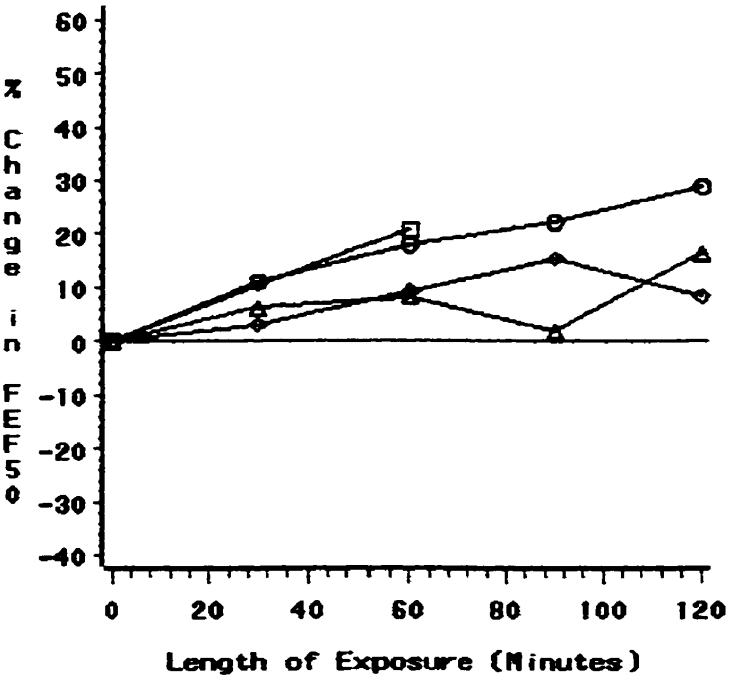

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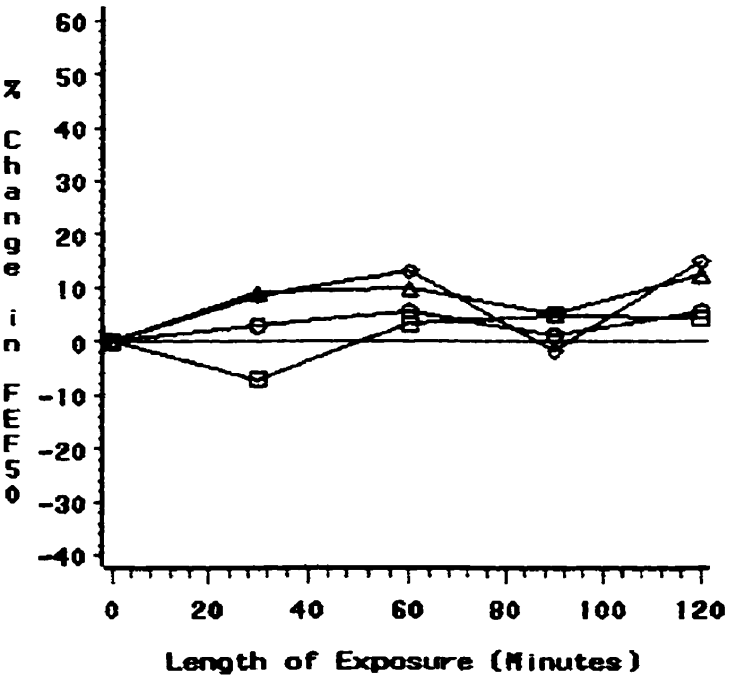

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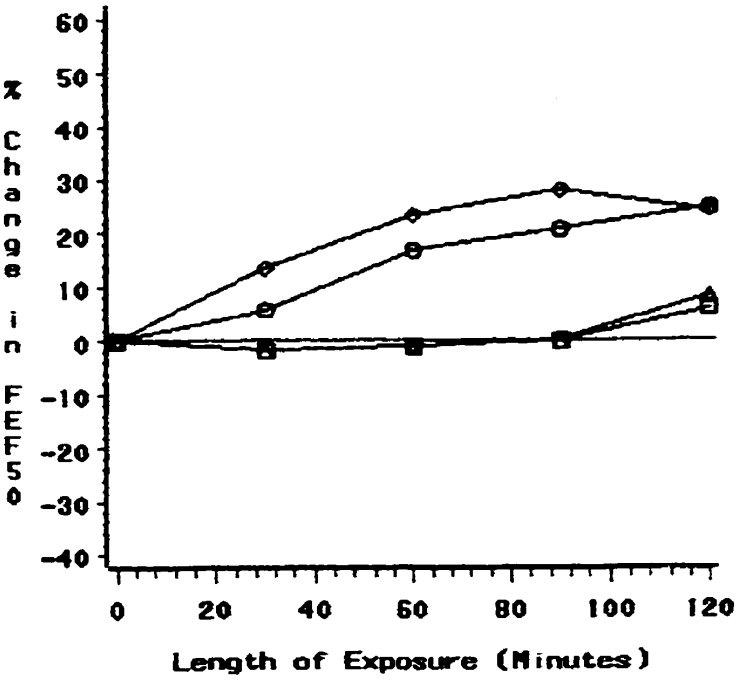

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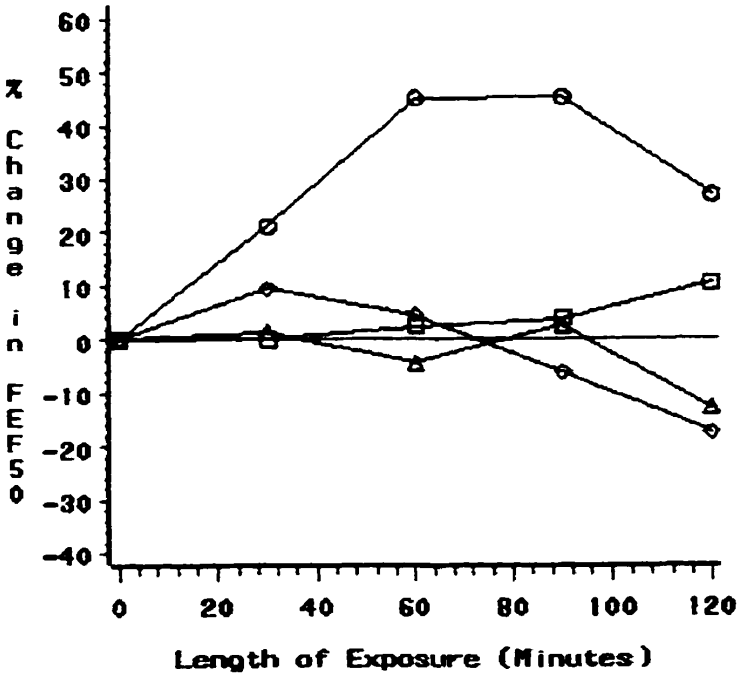

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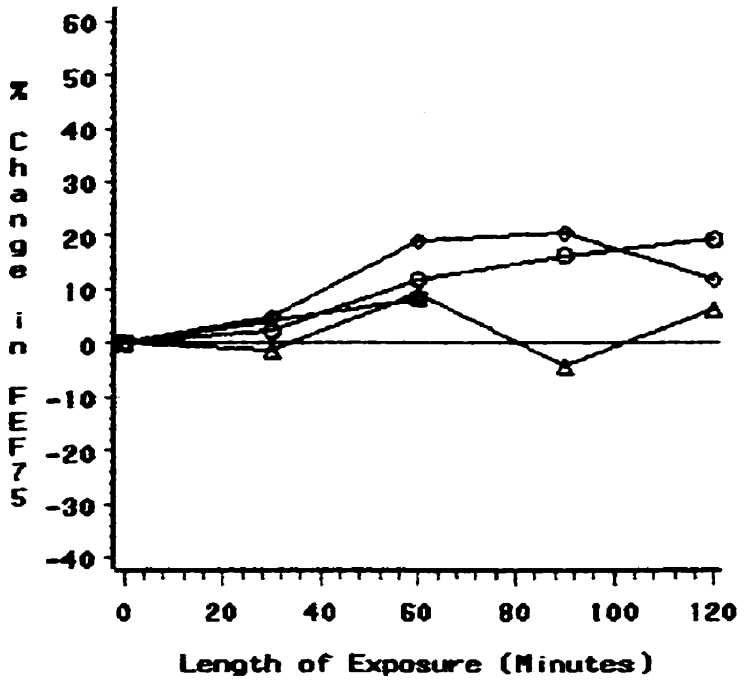

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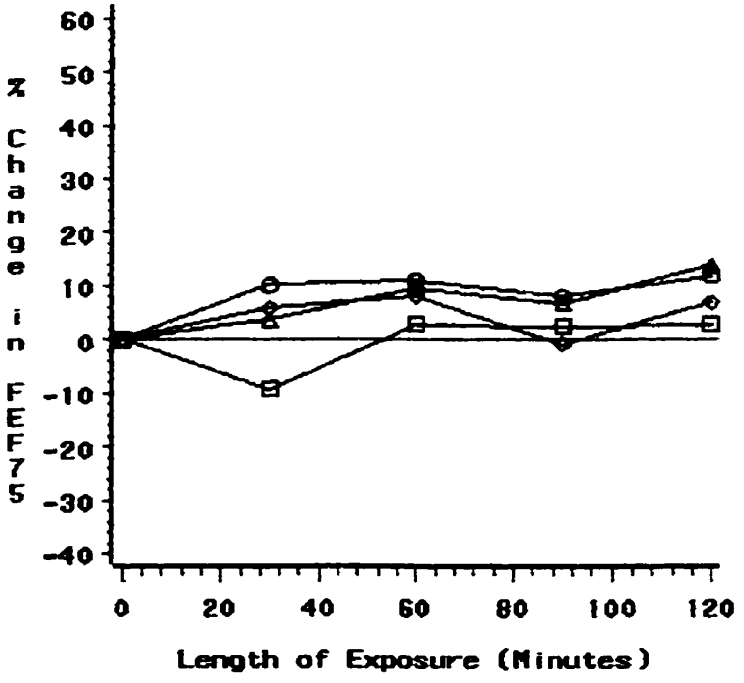

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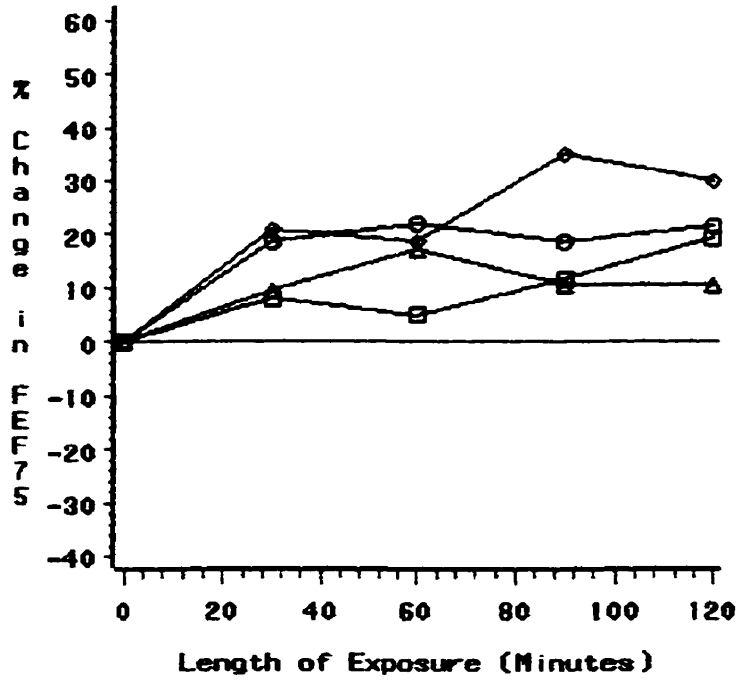

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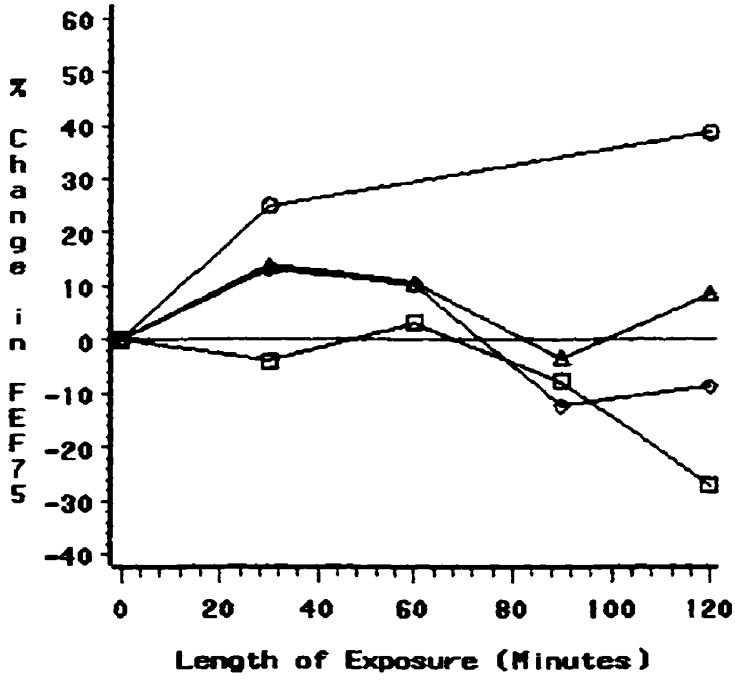

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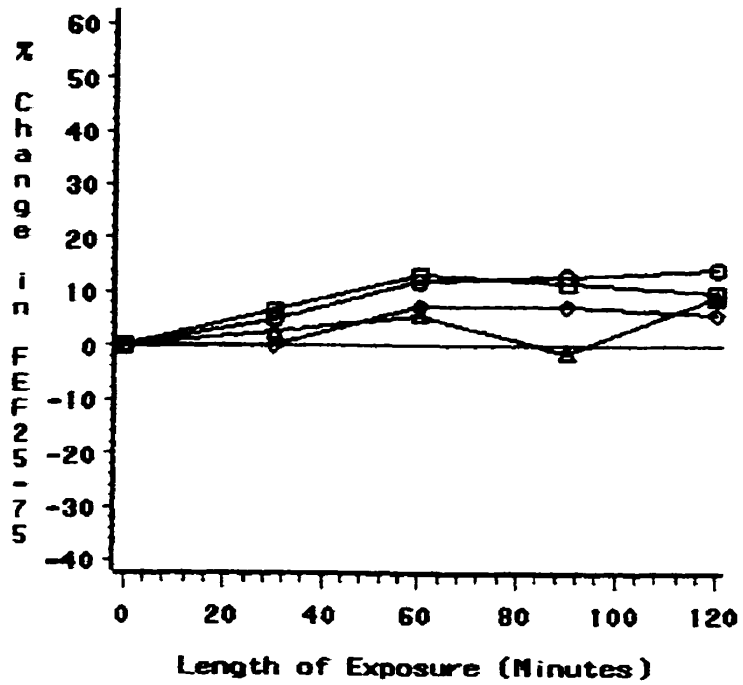

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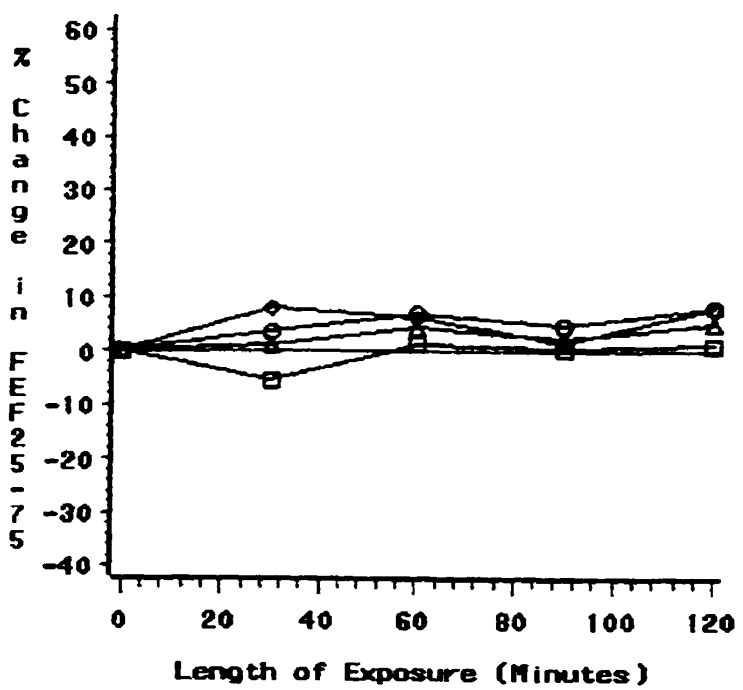

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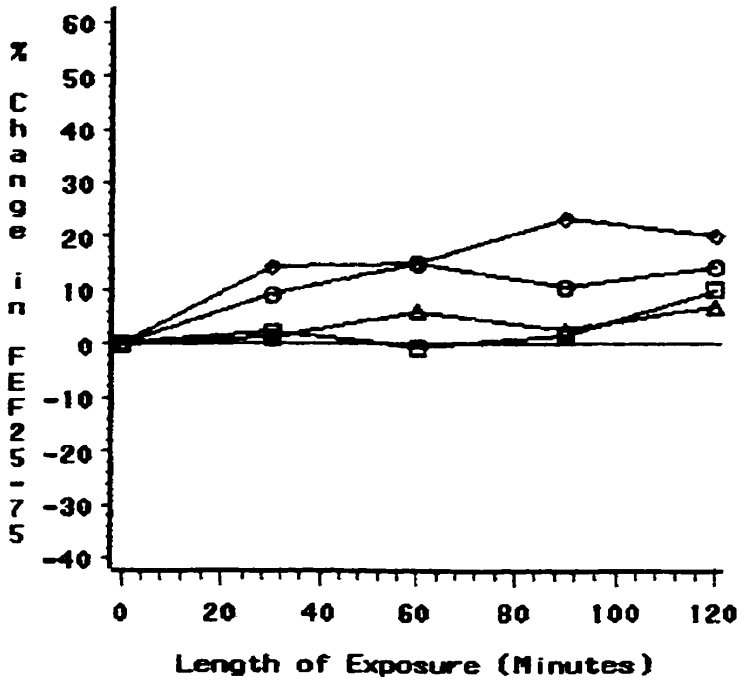

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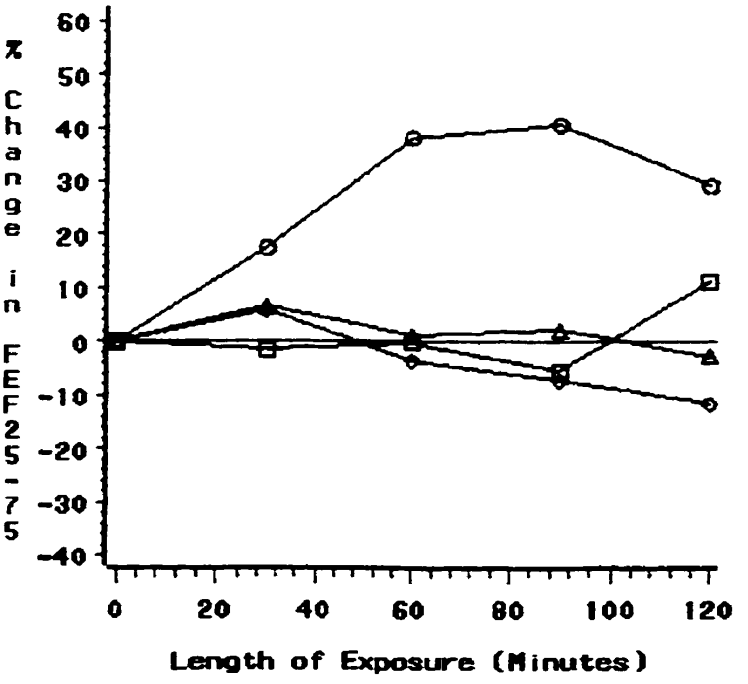

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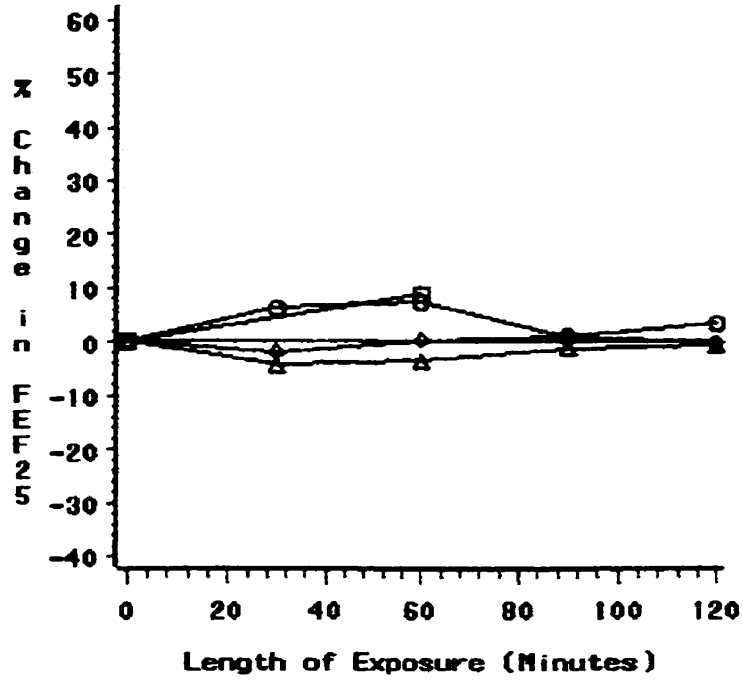

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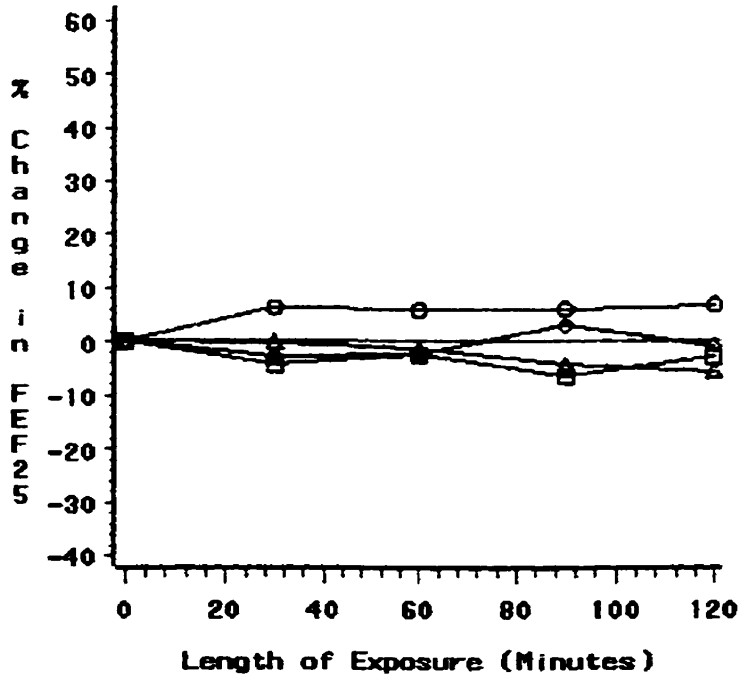

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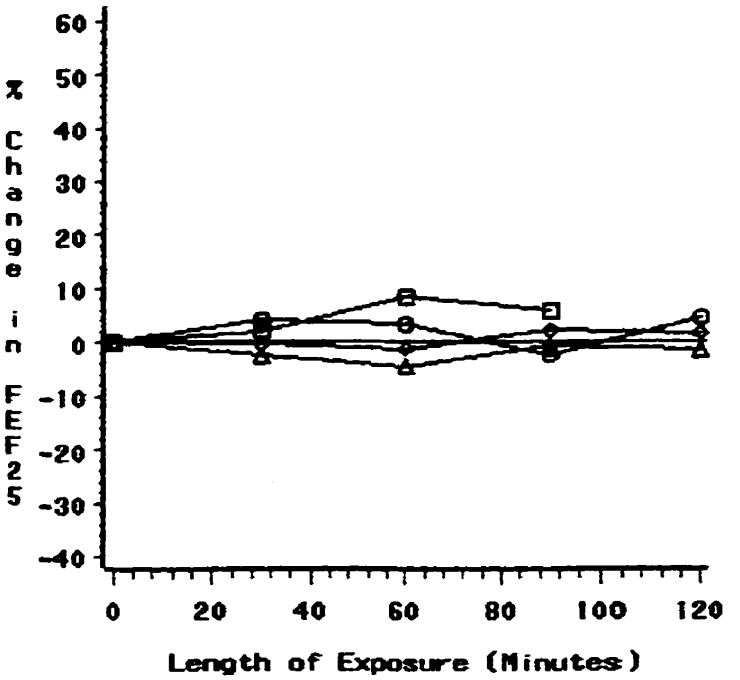

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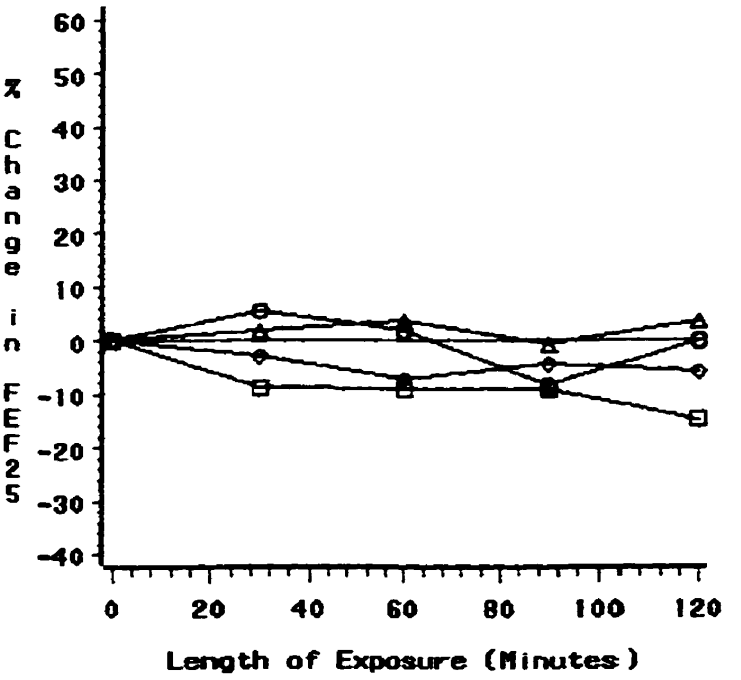

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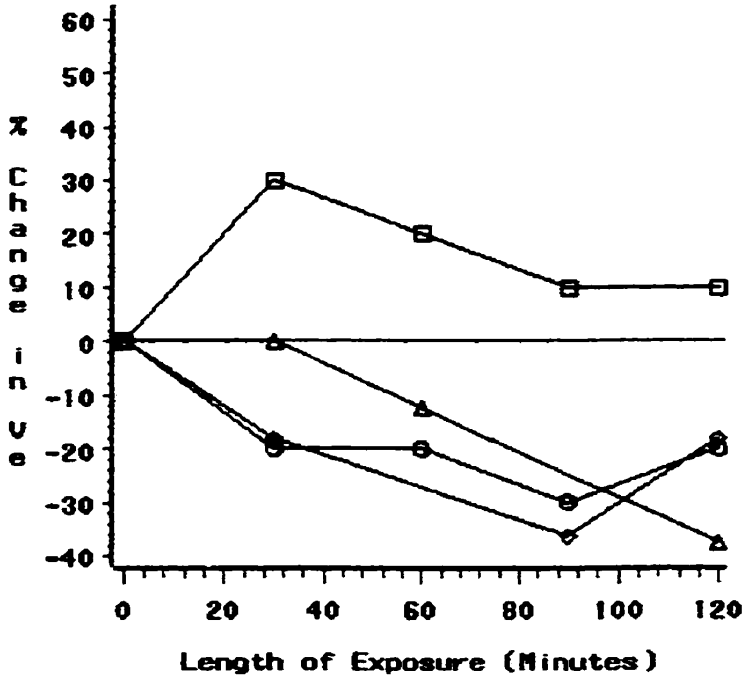

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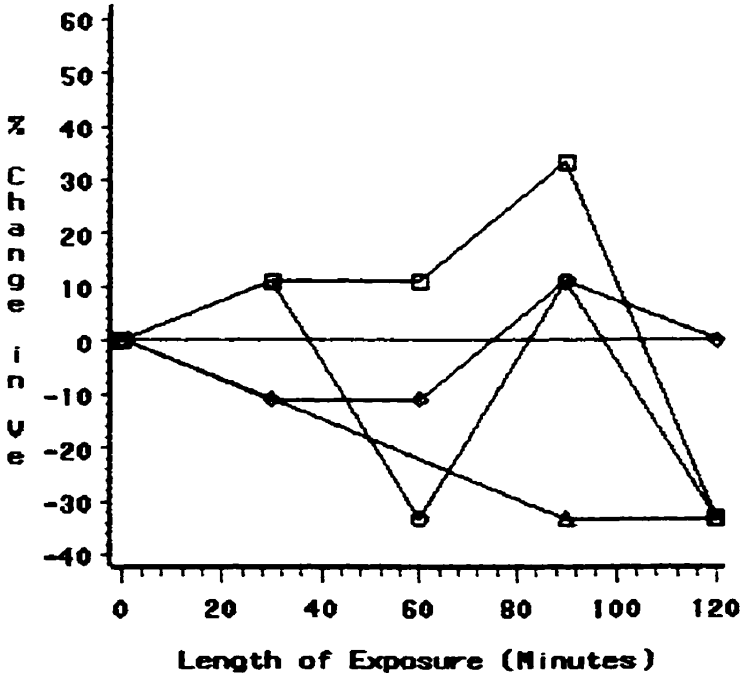

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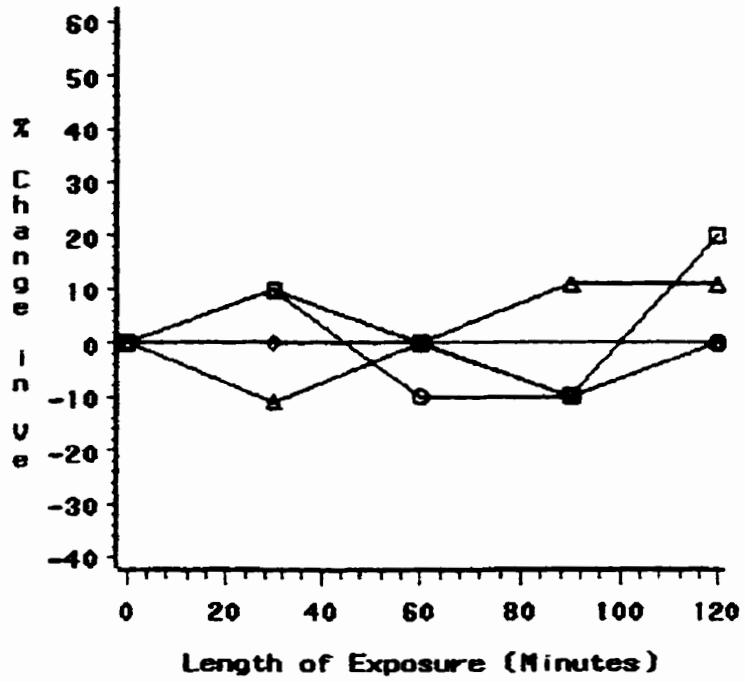

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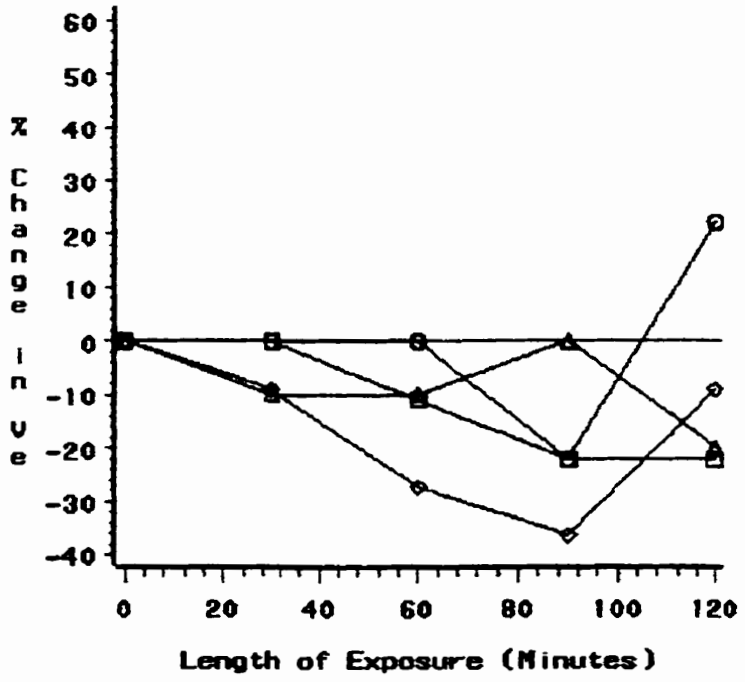

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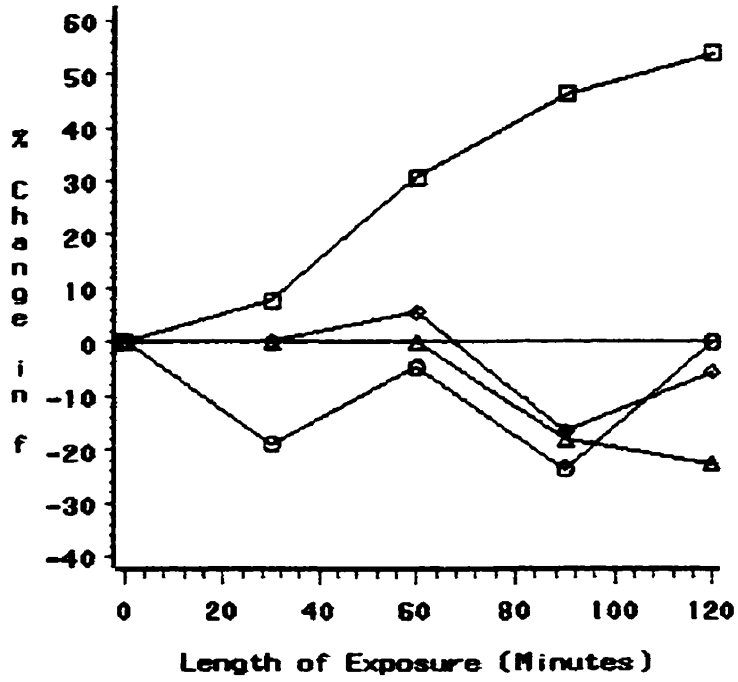

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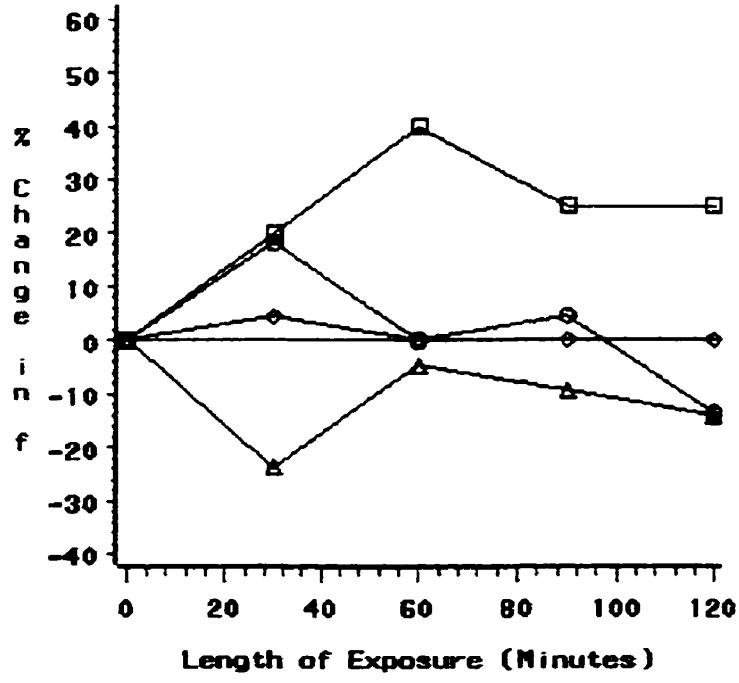

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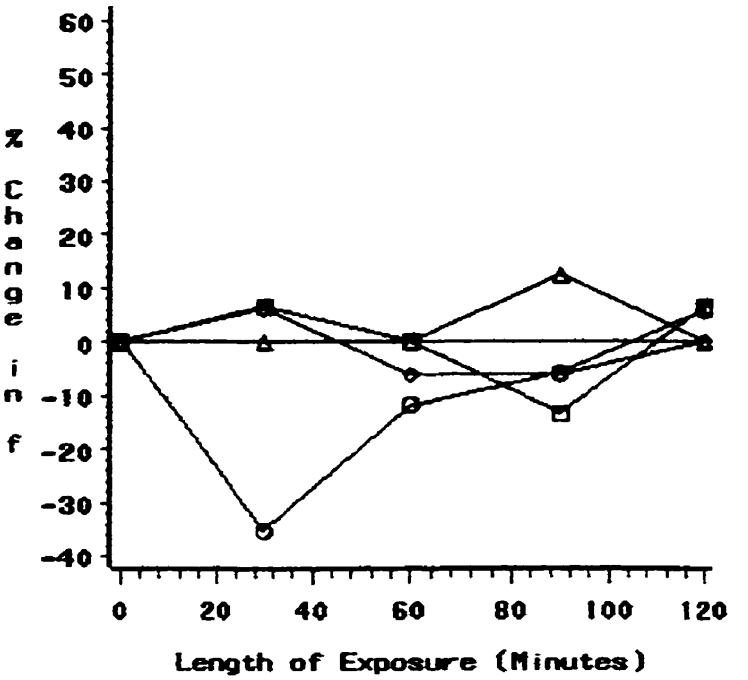

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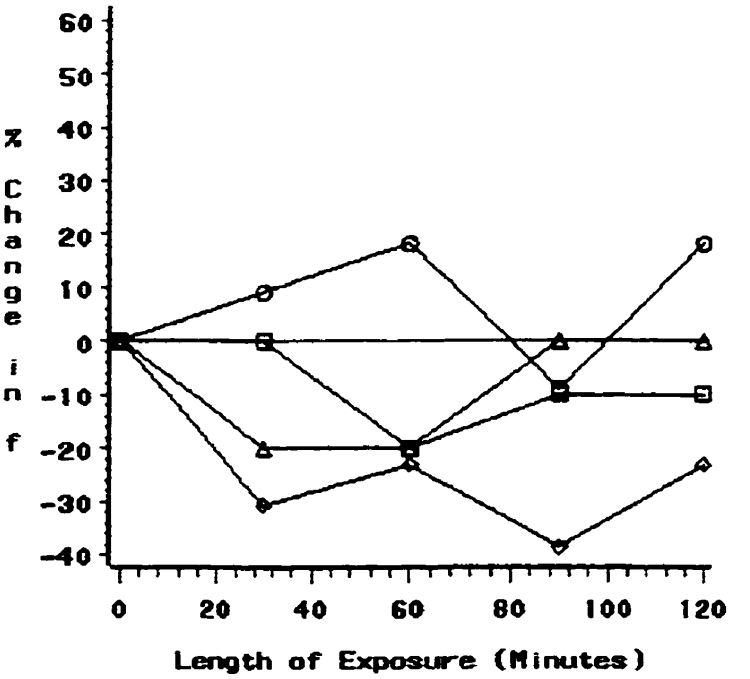

Target Exposure Conc. (ug/m3) 0 20 40 60

AIR POLLUTION STUDY VOLUNTEERS NEEDED

- to participate in air pollution study involving exposure to particles from outdoor air in our exposure facility at the GAGE Occupational and Environmental Health Unit (U of T)

- subjects must be 18-35 years of age, healthy, non-smokers, non-asthmatic, and able to do moderate to heavy exercise for 30 minutes on a stationary bicycle

THE GAGE OCCUPATIONAL & ENVIRONMENTAL HEALTH UNIT

CONTROLLED EXPOSURE TO AMBIENT PARTICLES

CONSENT FORM

It has been explained to me that a study is being performed to determine the effects of ambient air particles on the lungs, nose and heart. This study is being done using a special exposure facility at the Gage Occupational & Environmental Health Unit, in which the concentration of particles can be precisely regulated. The particles to be used will be those ordinarily present in Toronto air. The concentration of particles to be studied will be lower than the maximum levels that are sometimes found in the air of downtown Toronto and other places. Exposure of animals to high concentrations of particles have been reported to result in adverse health effects (specifically on the cardiorespiratory system); however, at the lower particle concentrations that will be used in this study, no adverse health effects have been reported in animals.

I understand that I will be visiting the Gage on nine separate days. On the first of these days, which takes about 4 1/2 hours of my time, I will complete a health questionnaire and receive a medical examination by one of the physicians at the Gage. Next, I will participate in a test of how irritable my bronchial tubes are, by inhaling increasing concentrations of a spray containing a drug (methacholine) that can narrow my bronchial tubes, in the same way as when a person gets asthma. This test is done by having me breathe in a weak solution of methacholine, that generally has no effect, and then gradually increasing the strength until a small effect occurs. The effect is measured by doing a brief breathing test after each strength of the spray is inhaled. The procedure is stopped as soon as there is a small temporary decrease in my lung function.

I will also participate in the following eight tests that are the basis of the study. These consist of the following:

i. a set of breathing tests;
ii. a test of the resistance to air flow through my nose, by sitting with my body inside a large box with my head outside the box and a seal around my neck. A very small tube will be inserted 8 cm into my nose, and then I will breathe through my nose with my mouth closed for 5 minutes;
iii. a measurement of the number and type of cells and biochemical compounds present in the fluids of my nose. I will be asked to squirt a mist of a salt solution into each of my nostrils using a syringe without a needle, to hold the solution in my nose for about 10 seconds, and then blow it out into a plastic specimen cup;
iv. electrocardiogram (ECG) monitoring of my heart, while I am lying down;
v. a questionnaire about my symptoms;
vi. I will be asked to allow one sample of blood of about 15 ml (one tablespoon) to be taken from my arm to measure how well my blood clots and to look at changes in the blood proteins that may have occurred as a result of being exposed to the air particles. The sample will be taken from a vein in my arm with a needle, as for standard blood tests. I understand that some slight bruising may occur in my arm, but no more than I may get when I have other routine blood tests done;
vii. I will exercise for 30 minutes on a stationary bicycle at 65% of my predicted maximum heart rate while wearing an ECG. My breathing rate and frequency will be measured with a breathing test every 10 minutes;
viii. a measurement of the number and type of cells and biochemical compounds present in my sputum. I will be asked to breathe air containing a salt solution for 7 minute periods for up to 21 minutes. Seven minutes after the start of the test and every 7 minutes thereafter, my breathing will be monitored by a short breathing test and I will be asked to rinse my mouth and throat and try to cough sputum into a

container. If troublesome symptoms occur during this procedure, the inhalation will be discontinued and an inhaled bronchodilator (Ventolin) will be immediately available to relieve my symptoms. Prior to starting this procedure, a short breathing test will be performed, and then I will be given an inhaled bronchodilator (Ventolin, 2 puffs, 200 micrograms). Ten minutes later, the inhalation procedure will begin. I am also aware that the most common complaint associated with this procedure is a salty taste in the mouth.

If I am found to be suitable for doing these tests, I will then be eligible to do the particle exposure studies. These involve coming to the Gage on four separate occasions, two weeks apart or longer, for about eight hours, and an additional four times, for about two hours of follow-up tests, the day after particle exposures. The particle exposure days will consist of my sitting for periods of two hours inside a large enclosed booth with three see-through windows. I will wear a small plastic "oxygen-type" mask which covers my nose, mouth, and chin. The particles, which are delivered to the nose area of the mask, will be precisely regulated. On one of the particle exposure days, the air delivered to the mask will consist of clean filtered air which has no particles. On the other three days, three different concentrations of particles will be added to the air delivered to the mask, on separate days, as follows: a low amount of particles; a moderate amount of particles; and a higher amount of particles. The order of my being exposed to the four different conditions will be mixed up, and I will not know which one I am breathing on a given day. Before and after each two hour particle exposure, I will complete tests i-v. A blood sample will be taken once before, and twice after a particle exposure. I will also complete tests vii & viii after each particle exposure. During each particle exposure, a breathing test will be repeated every 15 minutes, and I will wear several adhesive chest electrodes which will be used to monitor my heart rate and rhythm, that I will continue to wear during follow-up testing, after the particle exposure. The day after a particle exposure, I will come back to the Gage and repeat tests i, iii, iv, v, vi & viii.

All of the above procedures and tests are commonly done in respiratory research centers. I may experience some breathing difficulty during a methacholine test, but if this is troublesome to me, the test will be discontinued. Exposure to high concentrations of particles from ambient air have been reported to result in cough, shortness of breath, chest discomfort or headache. There is a possibility I may get a cold a few days following exposure. However, permanent health effects have not been reported from acute exposures to concentrations of particles that will be used in this study. We will monitor you continuously during exposure through windows in the enclosed booth. We will also monitor your heart rate and rhythm constantly during exposure and the 30 minute exercise period after exposure, for any possible adverse effects of exposure. If I have any trouble with the exposure or exercise, the test will be discontinued for that day. A physician will be available at all times. The physician will be equipped with suitable rescue medications to deal with possible adverse reactions, in case treatment is needed.

I agree to participate in this study, and understand that my participation is voluntary. All information collected from me will be kept confidential, and will not be divulged in a form that would identify my involvement. I may withdraw from the study at any time. I may contact one of the study physicians during the study, if I have any questions or adverse symptoms, and will be given their telephone number. I have been offered a copy of this consent form to keep.

_____	_____	_____	_____
Participant signature	print name	Witness signature	print name

Date:_____