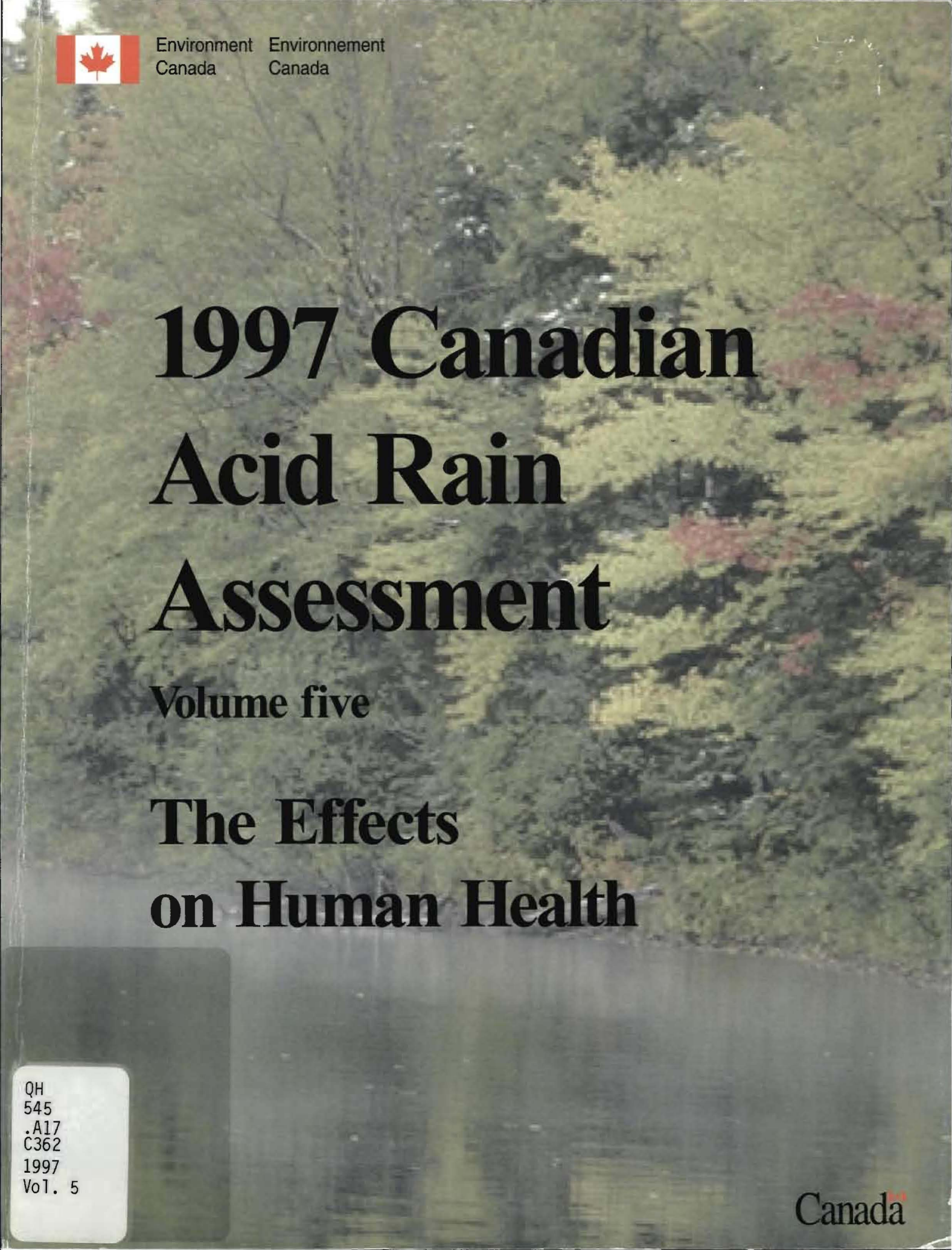

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The Effects on Human Health

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The Effects on Human Health

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The 1997 Canadian Acid Rain Assessment is a federal and provincial project that had its beginning at a joint meeting of the Canadian Council of Ministers of Environment and Energy in November 1994. At that meeting, the ministers agreed to develop a national strategy for a long-term acid rain program that would begin after the year 2000.

According to the statement of intent to which the ministers agreed, this strategy was to be based on consultations with Canadians and the principles of co-operation on which the ministers agreed the year before in the Comprehensive Air Quality Management Framework for Canada. The strategy also was to be founded on a scientific assessment of the progress made in existing programs as well as the adequacy of Canadian and American programs to protect Canadians' health and the country's ecosystems. This is part of that assessment.

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Executive Summary

The goal of this report is to provide a broad framework from the latest available data, most since 1990, in an attempt to estimate the specific agent(s) within the air pollution mixture of acid rain that is/are related to the adverse effects of human health. The direct and indirect health effects of sulphur dioxide (SO_2) and its derivatives, sulphate ($SO_4^=$), particulate matter (PM) and acid aerosols (H^+) are reviewed separately.

Review of Direct Health Effects: Summary for particulate matter, sulphate, and aerosol acidity-induced adverse health effects

Epidemiological studies

Mortality studies - Recent time-series and prospective cohort studies provide strong evidence for a link between ambient particle pollution and cardio-respiratory mortality. Such effects occur at ambient particulate levels below the present Canadian Ambient Air Quality Objectives for particulate matter (24 hour average Total Suspended Particulate Matter concentration 120 $\mu g/m^3$, annual geometric mean concentration 70 $\mu g/m^3$). The mortality increases monotonically with PM pollution levels, often with a near linear dose-response relationship, without obvious threshold.

The relative risk estimates of PM_{10} (particles with an aerodynamic diameter less than 10

μm) suggest a higher relative risk indicated for the elderly and for those with pre-existing compromised respiratory and cardiovascular conditions. These people may constitute subpopulations sensitive to the mortality implications of the exposures to PM pollution. As for children, it is difficult to ascribe any such association to PM pollution, given the limited and somewhat conflicting results available.

Although there is evidence from historical data that aerosol acidity may contribute to the associations between PM and human mortality, the key reactive component(s) of PM responsible for ambient particle-induced increases in mortality as yet remains undetermined.

Morbidity studies. - Recent studies conducted in various countries with different health care systems are suggestive of acute and chronic effects from PM pollution on respiratory and cardiac hospital admissions, respiratory symptoms and pulmonary function. The adverse effects were observed at ambient PM concentrations within the range of the Canadian Air Quality Objectives. The effects appear to be more significant in infants, elderly people, and in symptomatic groups such as asthmatics.

A series of recent studies conducted in 18 non-urbanized cities in the United States and 6 rural cities in Canada (the so-called "24-city study") has demonstrated that aerosol strong acidity and fine sulphate of PM may contribute to the respiratory symptoms and decrements in lung function observed in children (Spengler *et al.*, 1996, *Environ. Health Perspect.* 104:492-499; Dockery *et al.*, 1996, *Environ. Health Perspect.* 104:500-505; Raizenne *et al.*, 1996, *Environ. Health Perspect.* 104:506-514). Between 1988-1990, the respiratory symptoms of 13,369 caucasian children aged 8-12 years were reported using a parent-completed questionnaire. The pulmonary function of 10,251 caucasian children aged 8-12 years from the same 24-city was recorded. After adjusting for age, weight, height and the interaction of sex and height, associations were seen between increased reporting of bronchitis in the past year and particle strong acidity, and between the decrements of lung function and particle strong acidity, $PM_{2.1}$, $SO_4^=$, and PM_{10}.

As has been observed from the mortality studies, the risk of morbidity increased with PM levels, often in a near linear dose-response fashion, without obvious threshold. In some studies aerosol strong acidity appears to contribute significantly to the effects observed, while in others H^+ seems to have a threshold in initiating respiratory illness. It is difficult to separate the effect of PM from that of aerosol acidity, due to the strong collinearity between these pollutant measurements.

Clinical studies - The main purpose for performing human clinical studies is to evaluate the biological plausibility of adverse health effects of PM observed in epidemiological investigations. Available clinical study data indicate that, although the ranges of acid aerosol concentrations usually exceed those experienced by the general population, only mild decrements in pulmonary function have been induced in asthmatics, a susceptible subgroup. Elderly subjects and the subjects with COPD do not appear to be at higher risk to acid aerosol-induced impairment in pulmonary function than are younger subjects, even when doing mild exercise. No specific link between exposure to less acidic particles and the adverse health effects has been identified. No biochemical and physiological alterations in the cardiovascular system during controlled exposure have been reported.

These clinical observations cannot explain the changes of daily mortality and morbidity following the fluctuation of ambient particle levels that have been observed in epidemiological studies. Possible explanations for the discrepancy between clinical and epidemiological data may lie in as follows: (i) the experimental subjects can only be exposed to the tested air pollutants for short periods for practical and ethical reasons, while an urban pollution episode usually lasts a few days for general population exposure; a clinical study has shown that doubling the length of exposure to H_2SO_4 exerted greater effect on bronchial mucociliary clearance than did an order of magnitude increase in the concentration of H_2SO_4; (ii) the pulmonary function indices that are most often used in clinical studies may not be sensitive enough to indicate particle-induced adverse health effects; (iii) artificial aerosols and not atmospheric particles are given subjects in exposure chambers, which may not represent the possible synergestic effects of

PM and aerosol mixtures; (iv) in most human studies, the sizes of aerosols used were above 0.5 μm. Since nanometre-sized ultrafine particles have been found in animal studies to induce acute pulmonary inflammation and death at very low concentrations, and they are present in ambient air, ultrafine particles may, as suggested by Seaton *et al.* (1995, *Lancet* 345, 176-178), be "able to provoke alveolar inflammation, with release of mediators capable, in susceptible individuals, of causing exacerbations of lung disease and of increasing blood coagulability, thus also explaining the observed increases in cardiovascular deaths associated with urban pollution episodes". Currently, such mechanisms remain highly hypothetical.

Toxicological studies - Toxicological experiments exposing animals to "real world" polluted air have provided evidence indicating that chronic exposure to ambient air pollutants can result in pulmonary inflammatory effects. However the role of particles in producing these responses cannot be determined.

Non-acidic PM. - Studies utilizing non-acidic particles show that these particles generally have very low toxicity in inducing animal mortality and morbidity. High concentrations of PM are needed, often in the mg/m^3 range, to induce toxicity. However, comparative studies of particle exposure dosimetry in rats and humans have provided a fresh viewpoint. These studies suggest that PM-induced animal toxicity data may be relevant to observed associations between ambient PM exposure and human health outcomes, when taking into consideration the differences of airway geometry, minute ventilation rate, deposition efficiency, exposure term, and breathing fashion, between animals and humans.

The main mechanism for non-acidic particle-induced toxicity reported lies in the alteration of inflammatory mediator production, alteration of alveolar macrophage functions (often suppression of phagocytosis), and interaction with cellular macromolecules. It appears that the toxicity of PM depends largely on the acidity and size of particles. The evidence that surface-complexed iron and copper on particles can exert substantial inflammatory responses has provided more information in the mechanism by which non-acidic particles could provoke lung

injury. However, more information is needed concerning the toxicity of iron-containing particles at ambient levels. The findings on the susceptibility of diseased animals to particulate pollution are significant, but inconclusive evidence exists. More research is required.

Acidic aerosols. - Evidence shows that short term exposure to H_2SO_4 aerosol at the concentrations as low as 75 $\mu g/m^3$ can attenuate the release of reactive mediators that are involved in maintaining the reactivity of pulmonary alveolar macrophages. The biological mechanisms of H_2SO_4 are characterized as immunosuppression, bronchial hyperreactivity, and changes in mucociliary movement. There appears to be inter-species differences in terms of sensitivity to H_2SO_4-induced alteration of alveolar macrophage function.

Ultrafine particles. - Recent toxicological investigations using ultrafine particles (MMAD <0.06 μm), "real-world" particles with surface-complexed iron, and H_2SO_4-coated ultrafine metallic particles, have provided new insights for the nature of reactive components of PM. Because of the larger surface area of ultrafine particles, they may translocate into pulmonary interstitium to a greater extent, retain in the lung for longer period of time, and induce more severe pulmonary inflammation, when compared with fine particles. Moreover, studies using H_2SO_4-coated ultrafine zinc particles have demonstrated that ultrafine particles can potentiate the toxicity of H_2SO_4 synergistically. Since the toxicities of ultrafine particles, particles with surface-complexed iron, and H_2SO_4-coated ultrafine metallic particles all involve the stimulation of inflammatory mediators, it has been postulated that these particles may play an important role in exacerbations of lung disease and cardiovascular deaths associated with urban pollution episodes.

Ultrafine particles are constantly generated from combustion processes and from gas-to-particle conversion, and the ambient levels can exceed the concentrations used in the above animal studies. Therefore, the ultrafine particle model has provided an reasonable interpretation for the increased acute and chronic mortality and morbidity observed in sensitive subpopulation during episodes of elevated air pollution. However, very little information is available with regard to the exposure of general population to ambient levels of ultrafine particulate matter.

Summary for sulphur dioxide induced adverse health effects

Epidemiological studies regarding the associations between ambient SO_2 levels and human health effects have yielded apparently discrepant results that may be due to the differences in population compositions and in personal daily activities of those epidemiological investigations. Overall data have shown that the associations of daily SO_2 variations with daily mortality and morbidity rates are weak, and are readily confounded by other pollutants.

A few clinical studies have suggested that significant changes in pulmonary airway resistance may occur, at a concentration of 0.68 mg/m^3 or lower, in sensitive subjects such as asthmatics. Moreover, there is evidence that pre-exposure to 0.12 ppm of ozone can potentiate the sensitivity of asthmatic patients to SO_2.

Toxicological studies have shown very low toxicity of SO_2 in inducing animal pulmonary injury. Most toxic effects of SO_2 are observed at concentrations far beyond those normally encountered in ambient air. The main mechanisms observed for SO_2 toxicity lie in initiating the release of reactive oxygen-intermediates from pulmonary alveolar macrophages and peripheral blood mononuclear cells, and impairing mucociliary activity of airway ciliated cells.

Future research directions

(1). Further epidemiological studies need to be carried out to estimate public health impacts of ambient air pollution, including the impact on emergency department visits, hospitalization, pre-mature mortality, and the loss of life span (harvesting). The studies may be conducted on air pollution data obtained from representative areas with unique air pollution patterns, such as regions with high aerosol acidity but low PM levels, as well as other regions with just the opposite situation, in order to elucidate the potential key reactive component(s) of PM responsible for the increases in mortality and morbidity.

(2) Benefits and costs of controlling air pollution need to be estimated. Those types of studies will provide critical information for policy makers on the extent to which a variety of proposed programs to control air pollution represent good investments in the health of Canadians.

(3) Although epidemiological studies have raised a serious concern about public health effects of PM, questions that remain to be addressed relate to biological plausibility of the effects observed, host susceptibility, characteristics of particles, and contribution of other pollutants. Studies of controlled human exposure to PM may be conducted to define the mechanisms of PM-induced adverse effects.

(4) In order to identify subpopulations sensitive to the fluctuation of ambient PM pollution, an effort may be made to investigate the susceptibility of cardio-respiratory system-compromised patients in controlled exposure studies. This type of study may also help to elucidate potential interventions to protect people who are at greater risk.

(5) Personal monitoring should be carried out, in order to determine exactly what and when the elderly and susceptible populations are exposed, indoor and outdoor.

(6) Attention should be given to the human health effects induced by ambient ultrafine particles, iron-containing particles, and acid-coated ultrafine metallic particles, through epidemiological investigation and human clinical study. Since ultrafine particles represent a minor component of the total mass of ambient particles, but a major component of the total number of particles, the associations between particle numbers and sizes and the health effects require to be investigated.

(7) It is necessary to characterize physical-chemical properties of ambient ultrafine particles and their episodic fluctuation associated with specific meteorological conditions. Reliable instrumentation needs to be developed to quantify ultrafine aerosol in ambient air.

(8) More sensitive biomarkers for biologically effective dose and tissue injury should be introduced to link low PM exposure levels with the adverse health effects, in order to enhance the sensitivity of human clinical studies.

Review of Indirect Health Effects

The acid deposition, and acidification of water supplies and soil result in subsequent mobilization of heavy metals, which may increase exposure to these metals through drinking water and food. Of significant interest are cadmium, mercury, lead, arsenic, aluminum and chromium. In recent years, selenium has drawn an increasing interest as an important metalloid with industrial, environmental, biological and toxicological significance. Elevated concentrations of selenium in water samples in the United States have been noted at levels higher than U.S. EPA standard (10 ppb), which is associated with corrosion of household plumbing by soft, acidic water. Acute and chronic selenium toxicity has been observed in livestock and laboratory animals, involving various degrees of damage to internal organs, vascular edema, and heamorrage

In Ontario, elevated levels of dissolved copper, lead, and cadmium have been observed in water that was left undisturbed in distribution systems drawing water from privately supplied lake water. Northern Ontario, southwestern Ontario, the north shore of the St. Lawrence River in Quebec and areas of New Brunswick and Nova Scotia are areas in Canada that are very sensitive to acidification. An estimated 300,000 people in these areas obtain their drinking water from unregulated sources that may be affected by acid deposition.

The pollution of ambient particulate matter may cause visibility reduction. Particle-induced visibility reduction may affect climate by reducing solar radiation at ground level, making less energy available for photosynthesis. Reduced solar radiation may alter local or regional temperatures. Furthermore, increased cloud formation may alter precipitation patterns. These changes may result in damage to vegetation, which also indirectly affect the well-being of the entire human species.

1. Introduction

In 1990, the association between long-range transport of air pollutants and human health was reviewed by Federal/Provincial Research and Monitoring Coordinating Committee of Canada (RMCC)(Toxic Air Pollution-Health Effects Section, 1990). A considerable portion of the 1990 assessment focused on acid aerosols and ozone, since available toxicological and epidemiological evidence had demonstrated that many of the adverse health effects observed in epidemiological studies might be attributed to the mixtures of acid droplets. The report summarized the direct and indirect adverse health effects of acid aerosols and ozone from previous studies, and suggested that aerosol acidity was probably the most responsible for increased hospital admissions for respiratory conditions and decreased children's lung function. Limited monitoring data showed that the levels of acidic aerosols in southern Ontario could reach up to 250 $\mu g\ H^+/m^3$/day, which was equivalent to levels that could produce chronic bronchitis-like changes in rabbits. It may, however, be noted that due to the lack of specific aerosol acidity monitoring data at that time, it was difficult to clearly discriminate among those associated chemical species in acid rain concering the responsibility for the observed health effects. A number of epidemiological and toxicological studies have come to light during the first half of the 1990s. The results of these studies provide further evidence on the impacts of acid rain on human health.

The goal of this report is to provide a broad framework from the latest available data for attempting to estimate the specific agent(s) within the air pollution mixture of acid rain that is/are related to the adverse effects of human health. The public health impacts of particulate sulphates in Canada are also determined.

This report focuses on recently published studies, most since 1990. The direct and

indirect health effects of sulphur dioxide (SO_2) and its derivatives, sulphate ($SO_4^{=}$), particulate matter (PM) and acid aerosols (H^+) are reviewed separately. For convenience, these studies are subdivided into categories according to the evidence from epidemiological, clinical and toxicological studies. An effort is made in particular to underline the sensitive subpopulations who may be at greatest risk from exposure to air pollutants, and the possible reactive agent(s) responsible for adverse health effects, since they constitute a key issue in developing regulations for control of ambient air pollutant levels.

2. The Distribution of Sulphur Oxides across Canada

The air pollutants that are most related to acid rain are sulphur oxides and nitrogen oxides (NO_x). These substances interact in the atmosphere with sunlight and water to form acidic compounds [sulphuric acid (H_2SO_4) and nitric acid (HNO_3)] which can fall as acidic precipitation. Although nitrates, such as nitric acid, represent an important constituent of acid rain in the Northeast United States and Canada, their concentrations are significantly lower than sulphates. Therefore, this study will focus on sulphur-related pollutants, *i.e.*, sulphur dioxide (SO_2) and sulphates ($SO_4^=$) that are present as salts or H_2SO_4 in particles.

Sulphur dioxide is a primary pollutant that is released to the atmosphere from both natural and anthropogenic sources. Although there are many sulphur oxides in the atmosphere, SO_2 is the only one that occurs at significant concentrations. Although significant SO_2 emissions may occur from volcanic eruptions, anthropogenic sources are primarily responsible for most tropospheric emissions. The sources of SO_2 may be classified as mobile sources (including motor vehicles, aircraft, trains, ships *etc.*), stationary fuel combustion sources (including the generation of electricity from fossil fuels and residential, commercial, institutional and industrial space heating), and industrial processes (including mineral ore smelting, petroleum refining, etc.). Sulphur dioxide in the atomosphere converts to sulphuric acid (H_2SO_4). This is then gradually neutralized by ammonia (NH_3), first to a strong acid ammonium bisulphate (NH_4HSO_4), and then to ammonium sulphate [$(NH_4)_2SO_4$], a nearly neutral salt (Mellon *et al.*, 1986). H_2SO_4 and its neutralization products with ammonia, NH_4HSO_4 and $(NH_4)_2SO_4$, are all refered to as particulate sulphate.

Particulate matter can be classified as primary and secondary products. Primary products, usually coarse particles (larger than 2 μm in aerodynamic diameter), are mostly produced by mechanical processes and emitted directly into the atmosphere. Secondary products are formed in the atmosphere as a result of condensation of cold supersaturated low-vapour-pressure reaction products often generated photochemically, and are usually fine particles (less than 2 μm). Since fine particles (less than 2.5 μm in aerodynamic diameter, $PM_{2.5}$) can enter pulmonary tissue, they are considered to pose a greater health risk than coarser ones. The major component of $PM_{2.5}$ mass in many urban areas is sulphate, accounting for 40-50% of this fraction (Godish, 1991). Up to 80% of the PM_{10} (less than 10 μm in aerodynamic diameter) and 60% of the total suspended particles (TSP) are made up of $PM_{2.5}$. Although nitrates also are important component of ambient aerosol samples, their concentration is significantly lower than sulphates.

When solid or liquid particles are dispersed in the atmosphere, the resulting suspension is characterized as being an aerosol. The occurrence of acidic aerosols are linked to precursor emissions (such as SO_2 and NO_x). When $SO_4^=$ is initially produced it is in the form of H_2SO_4 which is gradually neutralized by ambient NH_3. The degree of neutralization depends upon the amount of NH_3 and acid particles encountered between the point of formation and the location of measurement and exposure. Various health studies have shown that physiologic responses to sulphate aerosols are dependent upon their acidity (Schlesinger, 1984; Schlesinger, 1989; Amdur, 1989; Schlesinger and Chen, 1994).

The levels of SO_2, SO_4, PM and acid aerosols in Canadian urban areas have been monitored by provincial and federal environment departments. In particfular, the National Air Pollution Surveillance (NAPS) data base and the Canadian Acid Aerosol Measurement Program (CAAMP) have collected and analyzed data relevant for human exposures and health effects research. These data are discussed in Sections 2.4.3 and 2.5.1 of the Atmospheric Science Assessment report, Volume 2 of this series.

3. Review of Direct Health Effects

Potential health effects of acid aerosols were reviewed in the 1990 Canadian Long-Range Transports and acid deposition assessment report (Toxic Air Pollution-Health Effects Section, 1990). The review reached the following conclusions:

(1) Animal toxicological studies showed that exposure of animals to H_2SO_4 at concentrations as low as 250 $\mu g/m^3$ caused bronchitis, by slowing of the clearance of particles out of the lung.

(2) Controlled human clinical studies demonstrated that acute effects of H_2SO_4 were more pronounced in asthmatics and occured rarely below 400 $\mu g/m^3$. One study conducted by Koenig *et al.* (1983) showed an acute effect of H_2SO_4 on lung function in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$. Effects in normal adults were not observed below about 900 $\mu g/m^3$.

(3) Human and animal laboratory studies of interactions between acid aerosols and ozone did not provide overwhelming evidence of possible synergism.

(4) From an epidemiological point of view, studies conducted in Canada showed that increased levels of acid aerosol, ozone and SO_2 were associated with decrements in children's lung function and a higher incidence of upper respiratory infections.

(5) Epidemiological studies also showed that daily pollution levels were associated with hospital admissions in summer for respiratory disease; this was proposed to be attributed to H_2SO_4 pollution, and combination effect of ozone and acids.

(6) Very little monitoring was carried out for acid levels in Canada.

This section focuses on the recent findings since 1990. The direct health effects of the

major components of acid rain, sulphur dioxide (SO_2) and its directives, are reviewed separately. These studies are subdivided into epidemiological, clinical and toxicological categories, in order to elucidate the evidence from human studies, and the biological plausibility. The possible sensitive subpopulation is discussed in detail, as they may be at greatest risk from exposure to air pollutants. An effort is made to underline the possible reactive agent(s) responsible for adverse health effects. The recognition of sensitive subpopulation and reactive agents are key components in leading to development of regulations for control of ambient pollutant levels.

3.1. Particulate matter, sulphate, and aerosol acidity

Particulate matter can be classified as primary and secondary products. Primary products, usually coarse particles (larger than 2.5 μm in mass median aerodynamic diameter, MMAD), are mostly produced by mechanical processes and emitted directly into the atmosphere. In North America, the major sources of particulate matter are vehicles, particularly those which are diesel powered, and residential heating (Godish, 1991). Secondary products are formed in the atmosphere as a result of condensation of cold supersaturated low-vapour-pressure reaction products generated photochemically, and are usually fine particles (less than 2.5 μm in MMAD). Particle size is believed to be the most important characteristic influencing deposition in the respiratory system (Lippmann, 1977; Hinds, 1982; Dockery and Pope, 1994). Since fine particles (less than 2.5 μm in MMAD, $PM_{2.5}$) can enter pulmonary tissue, they are considered to pose a greater health risk than coarser ones. Up to 80% of the PM_{10} (less than 10 μm in MMAD) and 60% of the total suspended particles (TSP) are made up of $PM_{2.5}$. The major component of $PM_{2.5}$ mass in many urban areas is sulphate, accounting for 40-50% of this fraction (Godish, 1991). Although nitrates are also an important component of ambient aerosol samples, their concentration is significantly lower than sulphates in most areas. Most $SO_4^=$ particles are of submicrometer size (MMAD 0.1 to 1 μm)(Lundgren and Burton, 1995). Particle clearance is achieved by the bronchial mucociliary movement when deposited in the trachea and bronchioles

to be expelled by coughing or swallowing, or by phagocytosis of alveolar macrophages when deposited beyond the terminal bronchioles. Once deposited on the airways, the biologic effects of particles are determined by the physical and chemical nature of the particles themselves and the substances adsorbed onto them.

Since $SO_4^=$ is the major component of respirable particulate matter, and is often acidic (Lundgren and Burton, 1995), the health effects of particulate matter, $SO_4^=$ and aerosol acidity are discussed together in this section. The evidence for potential critical reactive agent(s) in particulate matter, and potential sensitive subpopulation, will be discussed in this section.

3.1.1. Epidemiological data

The 1990 Canadian Long-Range Transports and Acid Deposition Assessment Report summarized that increased ambient acid aerosol levels were associated with decrements in children's lung function and an increase in incidence of upper respiratory infections. Daily pollution levels were associated with the hospital admissions in summer for respiratory disease, which was proposed to be attributed to H_2SO_4 pollution, and a combination effect of ozone and acids.

Since 1990, a wealth of data from time-series, cross-sectional and prospective cohort studies, and from acute and chronic exposure studies, form a cohesive hypothesis, showing associations between exposure to elevated levels of ambient air particulate matter pollution and various human health endpoints. It is noteworthy that the current most concerned results are for PM, while the acid rain-related pollutants ($SO_4^=$ and H^+) are only one component of PM. Short-term and chronic exposure to elevated levels of particulate matter has been reported to be associated with (i) increased mortality, especially cardiopulmonary mortality, (ii) increased hospital admission for respiratory and cardiovascular diseases, (iii) increased incidence and duration of respiratory symptoms, (iv) declines in lung function, and (v) restricted activity. Health effects have been observed at levels of particulate matter below current Canadian ambient

Air Quality Objectives (24 hour average 120 $\mu g/m^3$, annual geometric mean 70 $\mu g/m^3$).

In all epidemiological studies the major concern is that the observed association is due to confounding factors which are correlated with both pollution and health effect endpoints, when not adequately controlled for in the study design and analysis. For time-series studies, the basic potential confounders with the relationship between air pollution and daily mortality and morbidity are weather and infectious disease epidemics. Moreover, co-pollutants may also confound the outcomes due to their colinearity. Personal factors, such as diet, smoking, genetic predisposition, and occupational exposure, cannot induce a relationship between today's mortality and morbidity counts and yesterday's air pollution, since such factors are unlikely to vary on a daily basis in correlation with air pollution levels. For cross-sectional mortality studies, the opposite is true; differences in socioeconomic variables and occupational exposures are potentially serious confounders, while short-term weather patterns are of little concern.

3.1.1.1. Association with mortality

Table 3.1.1 (see end of chapter) summarizes the results from recently published epidemiological studies as to the associations between short term exposure to ambient levels of particulate matter and human mortality. Overall, consistently positive associations are seen between fluctuations in daily particulate levels and daily mortality throughout these analyses, despite the use of a variety of modelling approaches, and after controlling for major confounders such as season, weather and co-pollutants, with the 24-hour average 50 $\mu g/m^3$ PM_{10} total mortality effect estimate apparently being in approximately the RR = 1.025 to 1.05 range.

Table 3.1.1 also includes a population-based (ecologic) cross-sectional study that evaluated spatial distributions of mortality and air pollution (Ozkaynak and Thurston, 1987). The study found some association between long-term particulate air pollution and mortality on an annual average basis. However, this study did not address the effects of potential confounders, such as sex, smoking, ozone, SO_2, NO_2. Moreover, cross-sectional studies cannot determine whether the mortality associations are stronger for pollution measured the same year or in previous years. Cross-sectional studies cannot separate related chronic effects from the sum of

acute effects.

Two recent prospective cohort studies also have demonstrated increased mortality risks associated with air pollution. Since prospective cohort mortality studies can directly control for individual differences in confounding factors that are correlated with both exposure and mortality, such as age, cigarette smoking and occupational exposure, these studies provide some of the most compelling evidence about health effects. One of the most complete studies of the health effects of particulate matter pollution is the Harvard Six-Cities Study (Dockery *et al.*, 1993a). This was an extensive cohort study, involving 8111 adults over a 14 to 16 year follow-up period (between 1974 and 1989). After individual differences were controlled in age, sex, cigarette smoking, body mass index, education, and occupational exposure, the strongest associations were found between human mortality and $PM_{2.5}$ and $SO_4^=$. The association between mortality risk and $PM_{2.5}$ pollution was consistent, nearly linear, with no apparent "no effects" threshold level. Little or no association was found with the levels of total suspended particles, aerosol acidity, SO_2, or NO_2.

The above observation was supported by a second, larger prospective cohort study (Pope *et al.*, 1995). This study linked ambient particulate air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor data on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. When multivariate analysis was used to control for smoking, education and other risk factors, increased mortality was found to be associated with ambient $SO_4^=$ and fine particle air pollution at levels commonly detected in U.S. cities. This study supports the hypothesis of an association between fine particulate air pollution and human mortality, and corroborates the results from earlier cross-sectional studies.

Limited data obtained from Canada have provided similar evidence indicating positive PM-mortality associations. Ozkaynak *et al.* (1995) related total daily mortality in Toronto, over a 19 year period, 1972-1990, to daily PM_{10}, total suspended particles (TSP), $SO_4^=$, CO, ozone, temperature, and relative humidity. A 19-day moving average equivalent high-pass filter was used to prefilter out long-wave cycles in the data and to reduce autocorrelation. Ordinary least-square regression was employed, as the distribution of mortality data tend toward the normal in

larger cities such as Toronto (mean deaths = 40/day) once seasonal cycles are removed. In this dataset, 6,303 PM_{10} daily values were estimated based on TSP, $SO_4^=$, coefficient of haze (COH, a measure of fine black carbon particles), visibility, and temperature data, using a model developed from 200 actual PM_{10} sampling days during the study period. The simultaneous regression analyses of total mortality on both ozone and TSP or PM_{10} yielded significant coefficients for each pollutant. The estimated contribution of each pollutant to daily mortality at the mean pollution levels were 2.3% for either PM_{10} or TSP, and 1.5% for ozone. However, the authors found that it was not possible to separate the PM_{10}-mortality association from that for the other particulate matter metrics considered.

Sensitive subpopulation - A key issue in the evaluation of the health effects of air pollution is to identify the individuals who are at greatest risk from exposure to air pollutants. Schwartz compared the data of acute exposure to particulate air pollution, and cause and age of daily mortality in London during December 1952, and in Philadelphia, Pennsylvania, during 1973-1980 (Schwartz, 1994a). He found that the pattern of increased risk due to particulate air pollution versus age seen in the Philadelphia data was qualitatively similar to that seen in London. With the elevation of TSP concentration, the increased risk of deaths was greater in those aged 65 and older, greater for chronic obstructive pulmonary diseases (COPD), and greater for heart disease and stroke. These observations are supported by the earlier analyses by Schwartz and Dockery (1992a), who studied the daily cause-specific deaths between 1973-1980 in Philadelphia, Pennsylvania, and daily TSP levels. They found that the effect of 100 $\mu g/m^3$ TSP was stronger in subjects older than 65 years of age, and stronger in subjects with COPD, pneumonia, and cardiovascular disease. A recent study directly examining PM_{10}-mortality associations in the elderly was that by Ostro *et al.* (1995) in Santiago, Chile. For the general population, the RR estimate for 100 $\mu g/m^3$ of PM_{10} was 1.08, but in the case of the population aged 65 and greater, it rose to an estimate of RR = 1.11 in the same model specification. Thus, these directly comparable estimates suggest that the elderly experience roughly a 40% higher excess risk from exposure to PM air pollution than the general population. However, in a study

by Li and Roth (1995) who analyzed the daily mortality during 1973-1990 in Philadelphia County, no significant association was found between TSP and daily deaths in the elderly.

In the case of young children, Schwartz's analysis (Schwartz, 1994a) shows that no pattern of increased risk emerged until age 35 and above following the elevation of PM pollution in Philadelphia, although an increased mortality risk was seen in London in children under 1 year old. A recent analysis of PM_{10} pollution and mortality in São Paulo, Brazil provides further insight into the potential mortality effects of PM_{10} on children (Saldiva *et al.,* 1994). While there appears to be an association of NO_x pollution with respiratory mortality in children under 5 years of age in this case, no association was found between PM pollution and children's mortality.

Limited long-term exposure studies did not provide enough evidence as to sensitive subpopulation for mortality.

Overall, published data indicate that elderly people, and people "predisposed" with pulmonary and cardiovascular diseases may constitute a subpopulation who are more susceptible to elevated ambient particulate air pollution. This is consistent with airborne particles acting as a respiratory irritant to exacerbate pre-existing conditions, particularly respiratory conditions, although no exact pathophysiologic mechanism is known. As for children, it is difficult to ascribe any such association to PM pollution, given the limited and somewhat conflicting results available.

Reactive agent(s) responsible for PM-mortality association - The aerosol strong acidity has long been suspected as a specific chemical component of particulate matter responsible for the noted associations between particulate matter pollution and human health, due to their irritant and corrosive properties. Reanalysis by Thurston *et al.* (1989) of the London mortality data from 1963 to 1972 has shown that H_2SO_4 concentrations measured at the central site was much more strongly correlated with total daily mortality than any measure of British smoke or SO_2, especially when it was correlated with the next day mortality. The results from this study are supported by the investigation of Lipmann and Ito (1995). In this more extensive reanalysis of the London total mortality data where daily acid measurements were available year-round and the

air pollution levels were non-episodic, the authors separated each year into three seasons with restricted temperature ranges. It was found that there were relatively strong associations between daily mortality and the daily concentrations of H^+ and SO_2, whilst the associations with the daily British smoke were weaker. In a study conducted by Dockery *et al.* (1992), the authors attempted to relate present day ambient particle pollution with human mortality in St. Louis, MO and Kingston/Harriman, TN. The authors found only weak associations between total mortality and aerosol acidity, but strong associations with PM_{10}. However, because of the short monitoring period for daily H^+ concentrations, the authors concluded that the power of the study to detect associations was limited.

The relation between long-term exposure to ambient acid aerosol pollutants and human mortality also was investigated in prospective cohort studies. In the Harvard Six-City study (Dockery *et al.,* 1993a), very weak mortality associations were found with H^+, while the mortality associations with $PM_{2.5}$ and $SO_4^=$ were strong, after adjusting for smoking and other risk factors,. However, only less than one year of H^+ data were collected in each city, which is inappropriate when used to characterize lifetime exposures of adult study participants.

Therefore, because of the relative scarcity of direct acid aerosol measurements, at present findings on the associations between aerosol acidity and mortality are limited and highly variable.

In spite of the epidemiological evidence of the apparent association between aerosol acidity and human mortality, studies of industrial cohorts exposed to high concentrations of H_2SO_4 and other acid mists in steel-pickling operations show higher risk ratios only in lung cancer mortality when compared with general population; mortality from causes other than lung cancer is unremarkable (Beaumont *et al.,* 1987). One possible explanation may lie in the fact that the general population comprises a much higher proportion of people who, by reason of arteriosclerosis or chronic airway diseases, are at increased risk of death when subjected to environmental change than do industrial populations.

However, individuals at risk of mortality from particles would be expected to be indoors most of the time. It has been shown that indoor concentrations of H^+ and SO_2 are much lower

than those measured outdoors due to the neutralization by high concentrations of ammonia (NH_3) in indoor enviroment, whereas indoor $SO_4^=$ and NH_4^+ concentrations are almost as high as those found outdoors in the same general area (Brauer *et al.*, 1989; Suh *et al.*, 1993). As will be discussed in clinical and toxicological studies, much higher concentrations of H_2SO_4 than those typically detected in ambient air are required to induce mortality and morbidity. Therefore, aerosol acidity is not the sole critical component to which increased mortality is attributable. Very small particles within nanometre range readily penetrate indoors and persist for long periods in air. Toxicological studies have demonstrated that ultrafine particles (<50 nm in mass median diameter) at concentrations as low as 9 $\mu g/m^3$ can induce a series of pulmonary inflammatory responses and mortality in experimental animals. Moreover, since free radicals are involved during the generation of sulphate particles (Kao and Friedlander, 1995), ultrafine particles might serve as a possible marker or a surrogate for free radical exposure.

It is noteworthy that several investigations have reported that where appreciable particle strong acidity exists, virtually all exposures occur in the summertime (reviewed by Walkman *et al.*, 1995). This suggests more concern from particle strong acidity-induced health effects in the summer as opposed to other seasons, especially when taken into consideration that people spend much more time outdoor.

Summary for mortality studies - Recent time-series and prospective cohort studies provide strong evidence that ambient particle pollution can cause increased human respiratory and cardiovascular mortality. Such effects occur at ambient particulate levels below the present Canadian Ambient Air Quality Objectives for particulate matter. The mortality increases monotonically with PM pollution levels, often with a near linear dose-response relationship, without obvious threshold. The PM_{10} relative risk estimates derived from recent studies suggest a higher relative risk indicated for the elderly and for those with pre-existing compromised respiratory and cardiovascular conditions, who may constitute subpopulations sensitive to the mortality implications of the exposures to PM pollution. Although there is evidence from historical data that aerosol acidity may contribute to the associations between PM and human

mortality, the key reactive component(s) of PM responsible for ambient particle-induced increases in mortality as yet remains undetermined.

3.1.1.2. Association with morbidity

Exposure to elevated ambient particulate matter concentrations has been related to increased hospital admissions for respiratory and cardiac diseases (Table 3.1.2), increased incidence and duration of respiratory symptoms (Table 3.1.3), and declines in lung function (Table 3.1.4). (see end of chapter for all three tables.)

In Canada with a different medical care system from those in the United States and other countries, studies have indicated similar conclusions, namely, that daily fluctuations in ambient particle pollution are associated with cardiorespiratory morbidity.

Association with hospital admissions - Studies conducted by Bates and Sizto in southern Ontario before 1990 concluded that there was a consistent relationship between summer hospital admission due to respiratory diseases, and $SO_4^=$ and ozone, and that there was no relationship between respiratory admissions and SO_2 or summer haze levels (Bates and Sizto, 1983; Bates and Sizto, 1986; Bates and Sizto, 1987). They hypothesized that the adverse health effects were attributed to the aerosol strong acidity of the ambient particulate matter.

Since then, more studies have been carried out in Canada, which consistently support Bates and Sizto's observations. Lipfert and Hammerstrom (1992) used the same database as that of Bates and Sizto (1983, 1986, 1987) to analyze the association between air pollution (SO_2, NO_2, ozone, $SO_4^=$, TSP, and coefficient of haze) and respiratory illness including acute bronchitis, pneumonia, chronic bronchitis, emphysema, and asthma. Average pollutant concentrations were generally within the Canadian Ambient Air Quality Objectives and U.S. ambient standards. Bivariate correlations were calculated between pollutants and respiratory illness, and showed strong relationships between haze and its gaseous precursors. Pollutant-weather relationships were much weaker than the inter-pollutant correlations. According to stepwise multiple regression (a Box-Jenkins ARIMA multiple regression model), SO_2, ozone and

$SO_4^=$ aerosol were found to be significant predictors of respiratory admission during July - August.

Burnett *et al.* (1994) studied hospital admissions in southern Ontario, using a broader area than that used by Bates and Sitzo (1983, 1986, 1987). The respiratory admissions were for 1983-1988 and were restricted to acute bronchitis/bronchiolitis, pneumonia, chronic and unspecified bronchitis, emphysema, asthma, bronchiectasis, and chronic airway obstruction. The non-respiratory control admissions included non-respiratory cancer, and diseases of the blood and blooding forming organs, nervous system, circulatory system, digestive system, and genitourinary system. Daily ozone and $SO_4^=$ concentrations were obtained from three networks operating in the province: the Ontario Ministry of the Environment, the Air Pollution in Ontario Study, and the Canadian Air and Participation Monitoring Network. Slow-moving temporal trends in the admissions series, including seasonal and yearly effects, were removed by using a linear filter model. The estimates were obtained using the generalized estimating equations. Statistically significant positive associations were found between hospital admissions and both ozone and $SO_4^=$ recorded on the day of admission and up to 3 days prior to the date of admission. Ozone tended to be more significant than did $SO_4^=$ fraction. The model predicted about a 3% increase in respiratory hospital admissions for about a 14 $\mu g/m^3$ of $SO_4^=$ ambient concentration. Ozone and $SO_4^=$ were not related to non-respiratory control admissions, nor were they related to admissions in the winter months.

Thurston *et al.* (1994) reported the hospital admission data in the metropolitan Toronto area in July and August of 1986-1988. Pollution measurements included H^+, $SO_4^=$, ozone, NO_2, SO_2, $PM_{2.5}$, and PM_{10}. Long wave cycles, and their associated autocorrelations, were removed by first applying an annual periodicity sine-cosine fit to the data as well as day of week dummy variables and analyzing the resulting residuals. Ordinary least squares analyses were calculated after the environmental variables were detrended to eliminate the seasonal components. Regression analyses indicate that only the ozone, H^+ and $SO_4^=$ were associated significantly with respiratory and asthma admissions after controlling for temperature. When the compositions of particle matrix were compared for the strength of association with admissions, it appears

$H^+ > SO_4^= > PM_{2.5} > PM_{10} > TSP$, suggesting that particle size and composition are important in inducing adverse health effects.

Delfino *et al.* (1994) studied the urgent hospital admissions for respiratory diseases in Montreal during 1984-1988. Air pollution measurements included ozone, PM_{10} and $SO_4^=$ fraction of PM_{10}. A high-pass filter was used to eliminate yearly seasonal trends in the data. Potentially confounding day-of-week trends were controlled by prefiltering the outcome variables prior to analysis. Regression analyses with and without autoregressive terms show some indications of association between $SO_4^=$ levels and the non-asthma respiratory urgent hospital admissions in the July and August periods, and the association between PM_{10} and asthma admissions in the May-October periods.

Besides respiratory admissions, hospital admissions due to cardiovascular diseases have been studied as well. In a most recent study, Burnett *et al.* (1995) examined cardiac as well as respiratory admissions to 168 acute care hospitals in Ontario over the 6-year period 1983-1988. The specific cardiac diseases considered were acute myocardial infarction, angina pectoris, cardiac dysrhythmias, and heart failure. The respiratory diseases considered were asthma, bronchitis, emphysema, bronchiectases, chronic airway obstruction, acute bronchitis/bronchiolitis, and pneumonia. Daily exposure measurements included ambient $SO_4^=$ and ozone concentrations, and climate. Low-frequency temporal trends in the admission series, including seasonal variation in admission rates, were prefiltered by the 19-day linear filter. A 13 $\mu g/m^3$ increase in $SO_4^=$ recorded on the day prior to admission was associated with a 3.7% increase in respiratory admissions and a 2.8% increases in cardiac admissions. After adjusting for ambient temperature and ozone, similar results were observed. Excess respiratory admissions of 3.2% and a 2.8% were seen during April - September and during October - March, respectively. In the case of cardiac admissions, a 3.2% increase and a 3.4% increase were seen during April - September, and during October - March, respectively.

Almost identical outcomes were observed from a study of daily cardiovascular hospital admissions in Detroit, Michigan, 1986-1989 (Schwartz and Morris, 1995). The authors counted daily hospital admissions for ischemic heart disease, dysrhythmias and congestive heart failure of

elderly patients (aged 65 years and older). Daily PM_{10}, O_3, SO_2, CO and weather data were monitored. Poisson regression was employed to test the association on the same day and up to 2 previous days. Two-pollutant regression was tested to determine the independent contributions. After controlling for seasonal and other long-term temporal trends, temperature, and dew point temperature, an increase of PM_{10} of 32 $\mu g/m^3$ was demonstrated to be associated with daily admissions for ischemic heart disease (RR = 1.018, 95% CI 1.005-1.032), and for heart failure (RR = 1.024, 95% CI 1.004-1.044). CO also showed an independent association with heart failure admissions (RR = 1.022, 95% CI 1.010-1.034 for a 1.28 ppm increase in CO), but not with ischemic heart disease admissions. SO_2 and O_3 made no independent contribution to ischemic heart disease or congestive heart failure admissions.

Overall, hospital admission data from Canada and other countries with different medical care systems have demonstrated that admissions for both chronic obstructive pulmonary diseases and respiratory infections have a moderate but consistent association with particulate matter or its components. There is also evidence for a relationship between particulate pollution and cardiovascular diseases.

Association with respiratory symptoms and pulmonary function - In addition to hospital admissions, other indices including report of respiratory symptoms (Table 3.1.3) and pulmonary function (Table 3.1.4) (see end of chapter for charts) have been found to be related to changes of the levels of ambient PM pollution.

Several studies have been carried out in Canada in these areas. In an early study, Raizenne *et al.* (1989) examined acute lung function responses to ambient acid aerosol exposures in girls in a summer camp located in southwestern Ontario. Air quality measurements (ozone, H^+, $SO_4^=$, and $PM_{2.5}$) were performed on site and four distinct acid aerosol episodes were observed during the 41-day study. High degrees of correlation were indicated between $PM_{2.5}$, $SO_4^=$ and H^+, whereas temperature and relative humidity were weakly correlated with the air pollutants and each other, indicating that temperature and humidity were not likely to be major confounders in this analysis. Maximum decrements of 3.5% and 7% for FEV_1 and PEF,

respectively, were observed to be associated with the air pollution episodes. There was some indication that children with a positive response to a methacholine challenge had larger decrements in lung function compared to their negative methacholin-response counterparts, suggesting that children with hyperreactive airways are more susceptible to PM pollution. However, it was difficult to separate one pollutant from the other in terms of associations with lung function decrements, due to the strong intercorrelation.

In two cross-sectional studies conducted in Canadian communities (Stern *et al.,* 1989; Stern *et al.,* 1994), long-term exposure to ambient particle pollution have been related to children's respiratory symptoms and illnesses, and the alterations of lung function. Stern *et al.* (1989) compared the levels of PM_{10}, $SO_4^=$, particulate nitrates, SO_2, and NO_2 in Tillsonburg, Ontario, and in Portage la Prairie, Manitoba, in 1983-1984. Respiratory symptoms and diseases of the local children aged 7-12 were recorded using a parent-completed questionnaire. Lung function (FVC and $FEV_{1.0}$) of each child was measured. The levels of SO_2, $SO_4^=$ and particulate nitrates were significantly higher in Tillsonburg than in Portage la Prairie, but NO_2 and PM_{10} differed little between two communities. Concomitantly, Tillsonburg children had significantly lower levels of FVC and $FEV_{1.0}$ as compared with children in Portage la Prairie. With the exception of inhalant allergies which occurred significantly more frequently in Tillsonburg children, the prevalence of chronic respiratory symptoms and illnesses was similar in the two communities. The differences in the health outcomes observed between 2 communities could not be explained by parental smoking or education, the use of gas cooking or wood heating fuels, pollution levels on the day of testing, or differences in age, sex, height, or weight.

A more extensive study carried out by Stern *et al.* (1994) supported the above observations. Stern and the co-workers examined respiratory illness and lung function of school children aged 7-11 years in 10 rural Canadian communities. Five of the towns were located in southwestern Ontario (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg), a region with moderately elevated exposure to regional $SO_4^=$ and ozone; another five communities were located in central Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton), a low-exposure region. Pollution monitoring indicates that the concentrations of 1-h daily maximal

ozone and annual mean $SO_4^=$ in Ontario were substantially higher than in Saskatchewan, while PM_{10} levels or particulate nitrates were not significantly different. Levels of SO_2 and NO_2 were low in both regions. After controlling for the effects of age, sex, parental smoking, parental education, and gas cooking, no significant differences were observed in respiratory symptoms and illness between two regions. Nevertheless, children from southwestern Ontario had significant mean decrements of 1.7% in FVC and 1.3% in $FEV_{1.0}$ compared with Saskatchewan children. These two cross-sectional studies suggest that long-term exposure to elevated levels of $SO_4^=$ may be associated with moderate impairment of lung function in elementary school children.

A series of recent studies conducted in 18 non-urbanized cities in the United States and 6 rural cities in Canada (the so-called "24-city study") has demonstrated that aerosol strong acidity and fine sulphate of PM may contribute to the respiratory symptoms and decrements in lung function observed in children. Dockery *et al.* studied the respiratory symptoms of 13,369 white children aged 8-12 years between 1988-1990 using a parent-completed questionnaire (Dockery *et al.,* 1993b). Pollution of $PM_{2.1}$, PM_{10}, fine particulate $SO_4^=$ and acidity, and gaseous acids (nitrous and nitric acids) were monitored in these communities. Annual particle strong acidity was highly correlated with $SO_4^=$ and $PM_{2.1}$, but not with PM_{10}. A two-stage logistic regression model was used to adjust for the potential confounding effects of sex, history of allergies, parental asthma, parental education, and current smoking in the home, and to analyze the relationship between pollution measurements and the respiratory symptoms. Data show that there was a significant association between increased reporting of bronchitis in the past year and particle strong acidity (odds ratio = 1.66, 95% CI 1.11-2.48), and $SO_4^=$ (odds ratio = 1.65, 95% CI 1.12-2.42). No other respiratory symptoms were significantly increased in association with any of the air pollutants of interest.

Raizenne *et al.* (1993) studied the relationship between particle pollution and pulmonary function of 10,251 caucasian children aged 8-12 years from the same 24-city study. After adjusting for age, weight, height and the interaction of sex and height, associations were seen between the decrements of lung function and particle strong acidity, $PM_{2.1}$, $SO_4^=$, and PM_{10}. A

52 nmol/m^3 difference in particle strong acidity was associated with a 3.41% (95% CI -4.85 to -2.01) deficit in FVC and a 2.95% (95% CI -4.36 to -1.52) deficit in FEV_1, while a 15 μg/m^3 increase in $PM_{2.1}$ was associated with 3.21% (95% CI -4.98 to -1.41) deficit in FVC and 2.82% (95% CI -4.66 to -0.94) deficit in FEV_1. A 68 μg/m^3 increase in $SO_4^=$ resulted in 3.06% (95% CI -4.50 to -1.6) decrease in FVC and 2.63% (95% CI -4.18 to -1.05) decrease in FEV_1. The increase in PM_{10} levels also caused decrements in lung function, although to a less extent. A 17 μg/m^3 increase in PM_{10} was associated with 2.42% (95% CI -4.30 to -0.51) decrease in FVC and 2.09% (95% CI -4.00 to -0.14) decrease in FEV_1. The level of daytime ozone was also associated with the decrements of lung function. Nevertheless, controlling for daytime ozone did not significantly alter the association between FVC and particle strong acidity.

Sensitive subpopulation - Exposure to ambient particle pollution appears to have a differential effect on infants and elderly individuals. In a respiratory hospital admission study, Burnett *et al.* (1994) have shown that the largest impact of ozone-$SO_4^=$ pollution mix was on infants, and the least effects on the elderly. In another study regarding the relationship between $SO_4^=$ pollution and cardiac and respiratory admissions, Burnett *et al.* (1995) have demonstrated that admissions for cardiac diseases increased 2.5% for those under 65 years and 3.5% for those 65 years and older, following a 13-μg/m^3 increase in $SO_4^=$ concentration. These studies suggest that infants and elderly people may be more sensitive to elevated particle-related respiratory and cardiac admissions.

Pre-existing disease status may also potentiate particle pollution-induced adverse health effects. A cross-sectional study regarding the effect of particle pollution on respiratory health of school children in 6 cities of the United States demonstrates that children with a history of wheeze or asthma had much higher prevalence of respiratory symptoms in response to increased levels of PM_{15} (Dockery *et al.*, 1989) as compared with other children. The results are supported by a time-series study conducted for the daily changes in pulmonary function and the incidence of respiratory symptoms of grades 5 and 6 students in relation to the daily PM_{10} pollution in Utah Valley (Pope and Dockery, 1992). The data demonstrate that the association between the

decrements of lung function (PEF) and PM_{10} level was stronger for the symptomatic children than for the asymptomatic children. Likewise, the association between the incidence of respiratory symptoms and the PM_{10} level was larger in symptomatic children than in asymptomatic children. These associations were also observed at PM_{10} levels below the 24-h standard of 150 $\mu g/m^3$. Koenig *et al.* (1993b) reported similar results with respect to the respiratory function of 326 elementary school children in Seattle metropolitan area before, during and after the winter heating seasons. Their data indicate that asthmatic children had a greater response to elevated fine PM concentrations than did healthy children (Koenig *et al.*, 1993b). Therefore, children with hyperreactive airways may be particularly susceptible to other respiratory symptoms and pulmonary function changes when exposed to ambient particle pollution.

However, in the 24-city study, Dockery *et al.* did not find sensitive subgroups, after stratifying for sex, history of a severe chest illness before age 2, use of a humidifier in the home, lung function in the lowest quartile of FVC, current exposure to environmental tobacco smoke at home, exposure to maternal smoking during pregnancy, year of study, country and eastern versus western cities, to assess the evidence for the presence of sensitive subgroups (Dockery *et al.*, 1993b). The study of pulmonary function among the children in 24 cities did not identify the sensitive subpopulation either (Raizenne *et al.*, 1993).

Reactive agent(s) responsible for PM-morbidity association - Studies have demonstrated that strongly acidic PM can play a role in causing both acute and chronic respiratory illness. Thurston *et al.* (1992) and Thurston *et al.* (1994) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada. The study conducted in Toronto demonstrates that significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, ozone, in the regression model, and the increase in respiratory hospital admissions associated with H^+ was indicated to be roughly six times that for non-acidic PM_{10} (per unit mass)(Thurston *et al.*, 1994). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes ($H^+ \geq 10$ $\mu g/m^3$

as H_2SO_4, or ≈ 200 nmol/m^3 of H^+), which occur approximately 2 to 3 times per year in eastern North America.

Preliminary data from studies regarding the effects of long-term acid aerosol exposure on children's respiratory health and lung function indicate that bronchitis prevalence rates as reported across the 6 cities in the United States were more closely associated with average H^+ concentration than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh community which controlled the analysis for maternal smoking and education, and for race, suggestes associations between summertime average H^+ and chronic bronchitis and related symptoms (Damokosh *et al.,* 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmol/m^3 of H^+) versus the lowest concentration (16 nmol/m^3 of H^+) was 2.4 (95% CI: 1.9-3.2). In the 24 U.S. and Canadian city study, particle strong acidity appeared to have the strongest association with the decrements of lung function (Raizenne *et al.,* 1993), and children living in the community with the highest levels of particle strong acidity were more likely to report having had at least one episode of bronchitis in the past year compared to children living in the least polluted community (odds ratio = 1.66, 95% CI 1.11-2.48)(Dockery *et al.,* 1993b). Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children.

However, in the 6-city study of diaries kept by parents of children's respiratory and other illness, ambient H^+ concentrations were not found to be associated with respiratory symptoms until above 110 nmol/m^3, while a significant association was seen between respiratory symptoms and PM_{10} concentration (Schwartz *et al.,* 1994). Unlike PM_{10} which shows non-threshold linear correlation with upper and lower respiratory symptoms, there appears to be a threshold for H^+ (110 nmol/m^3) based on statistical analysis of these data to exert its adverse health effects (Schwartz *et al.,* 1994).

In a case-control study conducted in southern Ontario, Canada, occupational exposure to H_2SO_4 in association with laryngeal cancer was assessed (Soskoline *et al.,* 1992). The cases were individually matched to neighborhood referents for gender and age. H_2SO_4 exposure for each job was retrospectively assessed, blind of disease status. When tobacco and alcohol were

controlled H_2SO_4 exposure-response gradients were significantly positive, with odds ratios in the range of 1.97 (95% CI 0.63-6.13) for short duration-low level exposure, and 6.91 (95% CI 2.20-21.74) for long duration-higher level exposure. Asbestos and nickel was not found to be a significant confounder.

Since most studies have indicated a strong intercorrelation between aerosol strong acidity and fine particles or $SO_4^=$, it is very difficult to separate the effect of one from the other. As will be discussed in toxicological study section, H_2SO_4 coated on ultrafine metal particles (mass median average diameter >50 nm) can cause much greater airway injury in animals than does the same concentration of H_2SO_4 alone. It is possible that ultrafine respirable PM plays a critical role as a carrier for the acids. It is likely that the ultimate toxicity of ambient PM is attributed to the joint effects of particle sizes, particle acidity, and free radicals on the surface of these particles generated during the transformation of sulphate particles (Kao and Friedlander, 1995).

Summary for morbidity studies.

Recent studies conducted in various countries with different health care systems are suggestive of acute and chronic effects from PM pollution on respiratory and cardiac hospital admissions, respiratory symptoms and pulmonary function. The adverse effects were observed at ambient PM concentrations within the range of the Canadian Air Quality Objectives. The effects appear to be larger in infants, elderly people, and in symptomatic groups such as asthmatics. As has been observed from the mortality studies, the risk of morbidity increased with PM levels, often in a near linear dose-response fashion, without obvious threshold. In some studies aerosol strong acidity appears to contribute significantly to the effects observed, while in others H^+ seems to have a threshold in initiating respiratory illness. It is difficult to separate the effect of PM from that of aerosol acidity, due to the strong collinearity between these pollutant measurements.

3.1.2. Clinical data

Human clinical studies utilize controlled laboratory atmospheric conditions, and document the health effects that result from breathing the controlled atmospheres. There are some advantages in performing clinical studies. Since the atmosphere is highly controlled for individual pollutants, in a dose-response manner, it can be used to characterize an exposure-response relationship. Such a controlled environment provides the opportunity to examine interactions among pollutants or with other environmental variables such as humidity, temperature or exercise. Subjects from special subpopulations, such as young children or elderly people, asthmatics or patients with chronic obstructive pulmonary diseases, may also be studied to identify potentially susceptible subpopulations. The limitations of clinical studies lie in the practical and ethical aspects. Clinical studies have to be limited to short durations and only concentrations of pollutants that are expected to produce mild and transient responses. An endpoint assessment has to be relatively non-invasive, and invariably includes pulmonary function, which sometimes may not be sensitive enough to reflect the adverse effects. Furthermore, transient responses in clinical studies have never been validated as predictors of more chronic and persistent effects. Nevertheless, controlled, quantitative clinical studies provide a complementary approach to examine the biological plausibility of the associations that has been observed in epidemiological investigations.

The 1990 Canadian Long-Range Transports and Acid Deposition Assessment Report summarized that the acute effects of H_2SO_4 on humans were more pronounced in asthmatics and occurred rarely below 400 $\mu g/m^3$, whereas effects in normal adults were not observed below about 900 $\mu g/m^3$ (Toxic Air Pollution-Health Effects Section, 1990). Table 3.1.5 (see end of chapter) summarizes the recent data from human clinical studies as to PM-induced health effects.

3.1.2.1. Sensitive subpopulation

Overall results from recent studies are consistent with those reported in the 1990 assessment, and indicate that healthy subjects are not sensitive to short-term exposure to acidic or non-acidic aerosols, or polluted air mixture. For example, when healthy subjects inhaled for 2 h H_2SO_4 aerosols at 1000 $\mu g/m^3$, which is much higher than the concentrations in ambient air, with intermittent exercise, they generally did not show inflammatory responses in bronchoalveolar lavage fluid (Frampton *et al.,* 1992). Exposure of healthy volunteers to bagged polluted air containing TSP, SO_2 and NO_2 (202 $\mu g/m^3$, 112 ppb and 488 ppb, respectively) for 30 minutes did not show any alteration of pulmonary function and bronchial reactivity to methacholine challenge (Yang and Yang, 1994). On the other hand, asthmatic subjects did show significant decreases in lung function and an increase in airway reactivity in response to inhalation of bagged polluted air (Yang and Yang, 1994). Utell and co-workers studied the effects of sequential H_2SO_4 and ozone exposures on the pulmonary function of healthy and asthmatic subjects (18 - 45 years of age) (Utell *et al.*; 1994). The subjects were preexposed to H_2SO_4 (100 $\mu g/m^3$) or NaCl control, and 24 hours later, exposed to ozone (0.08, 0.12 or 0.18 ppm), with intermittent exercise. For the healthy group, no significant symptomatic or physiologic effects of exposure to either aerosol or ozone on lung function were found, and no interaction between aerosol and ozone exposures was found. For the asthmatic group, preexposure of H_2SO_4 had no direct effect on lung function, but appeared to enhance the small mean decrements in FVC in response to 0.18 ppm ozone.

It was also observed that brief exposure to as low as 35 $\mu g/m^3$ of H_2SO_4 aerosol induced a mild decrement of lung function and an increase in total respiratory resistance in allergic adolescent subjects (Koenig *et al.,* 1989) and asthmatic adolescent subjects (Koenig *et al.,* 1992; Hanley *et al.,* 1992). The lower range of H_2SO_4 concentration is around the peak values measured during the summer months in the eastern United States and southern Canada. Since adult asthmatics have not been reported to respond significantly to similar doses of H_2SO_4 via the same exposure procedure (Utell *et al.,* 1994; Aris *et al.,* 1990; Aris *et al.,* 1991b), it seems that adolescent asthmatic subjects are more susceptible to H_2SO_4 insults.

It has been noted that in severe stages of pulmonary diseases, a small portion of the lung volume receives most of the tidal breathing volume (Bates, 1989). Miller *et al.* (1995) thus suggest that localized overload of particulate clearance mechanisms may occur in patients with severe lung diseases, which may further compromise the ability of the lungs to satisfy the ventilatory needs, thereby leading to enhanced morbidity or death.

Similar results have also been observed in elderly subjects aged 60-75 years (Koenig *et al.*, 1993a). When elderly normal and asthmatic volunteers inhaled H_2SO_4 or $(NH_4)_2SO_4$ (70 $\mu g/m^3$, MMAD 0.6 μm) for 40 minutes with mild exercise, a significant increase in total respiratory resistance was seen in the asthmatic subjects but not in normal subjects (Koenig *et al.*, 1993a). However, compared with younger subjects under the similar H_2SO_4 dose regime (Koenig *et al.*, 1992), elderly subjects do not appear to be more at risk for adverse respiratory effects from inhalation of acid aerosol.

Based on the epidemiological observations, subjects with COPD are considered to be potentially at high risk for mortality and morbidity from particle pollution. Morrow *et al.* (1994) studied the pulmonary function of the subjects with COPD in response to low levels of H_2SO_4 aerosol (90 $\mu g/m^3$) for 2 hours. Subjects (mean age = 62 years) were defined by dyspnea on exertion, obstructive airway disease and a lack of response to bronchodilators. In contrast to findings in asthmatic patients, the COPD subjects did not demonstrate significant decrements in pulmonary function in response to H_2SO_4, even with mild exercise during exposure periods.

Collectively, the findings of these studies provide evidence that subjects with asthma or allergy differ from healthy volunteers in pulmonary functional responses to exposure to H_2SO_4, or sequential exposures to H_2SO_4 aerosol and ozone, albeit the responses were small. Hence, asthmatic and allergic subjects may represent a susceptible subpopulation. Adolescent asthmatic subjects appear to be more sensitive to ambient levels of acid aerosol than adult asthmatics. by evaluating pulmonary function changes, there is no sufficient evidence that elderly subjects or COPD patients are more sensitive to the inhalation of acid aerosol. There is no report on the sensitivity of subjects with compromised cardiovascular function to controlled PM inhalation.

3.1.2.2. Reactive agent(s) responsible for association between ambient particulate matter and health effects.

Human clinical studies of particle exposure remain almost completely limited to the study of acid aerosols, primarily of H_2SO_4. Human studies of particles other than acid aerosols provide insufficient data to draw conclusions regarding health effects. The limited data have suggested that the $SO_4^=$ is not the biologically active portion of particulate sulphate species. For example, a study by Utell *et al.* (1983) demonstrates that controlled exposure of asthmatic patients via a mouthpiece to non-acidic $(NH_4)_2SO_4$ aerosol concentrations up to 1000 $\mu g/m^3$ (MMAD 0.8μm) for 16 minutes did not cause pulmonary function change (Utell *et al.*, 1983). On the contrary, short time inhalation of H_2SO_4 at concentrations as low as 35 to 51 $\mu g/m^3$ caused mild pulmonary function impairment in asthmatic adolescents (Koenig *et al.*, 1992; Hanley *et al.*, 1992). The exposure concentrations are near the peak values detected during the summer months in eastern North America, which supports the epidemiological observations that fluctuation of ambient particle concentration can result in exacerbation of asthma. Studies conducted by Utell *et al.* (1989) and Hanley *et al.* (1992) have shown that depletion of oral ammonia with acidic drinks exaggerated the subsequent pulmonary response to inhaled H_2SO_4, providing further evidence that aerosol acidity plays an important role in sulphate particle-induced decrements in lung function.

In addition to inducing acute decrease in pulmonary function, inhalation of H_2SO_3 has been found to cause delayed bronchial mucociliary clearance in healthy subjects (Spektor *et al.*, 1989). When healthy, nonsmoking subjects were exposed to 100 $\mu g/m^3$ of H_2SO_4 aerosol for 1 or 2 hours, they showed significantly prolonged half time of tracheobronchial clearance for γ-tagged ferric oxide particles compared with exposure to control (water aerosols), although the pulmonary function was not significantly affected. These data indicate that the indices of lung function may not be sensitive enough to reflect low concentrations of H_2SO_4-induced airway injury in healthy subjects as observed in a series of clinical investigations, even when low concentrations of H_2SO_4 have impaired tracheobronchial mucociliary clearance function which is

a critical pulmonary defense mechanism. The damage of tracheobronchial mucociliary clearance function renders the subjects vulnerable to the attack by infectious microorganisms or air pollutants. Moreover, the data show that the effect of doubling the length of exposure was as great or greater than a 10-fold increase in the concentration of H_2SO_4.

Respirable particles are suspected to increase the pulmonary toxicity of acidic pollutants by concentrating acid on their surfaces and so delivering it efficiently to the deeper respiratory tract. Anderson *et al.* (1992) used the respirable carbon and H_2SO_4 to test the hypothesis that inert particles in ambient air may potentiate the pulmonary toxicity of co-existing acidic aerosols. Carbon aerosols were generated from highly pure carbon black with specific surface area comparable to ambient pollution particles. Healthy and asthmatic subjects were exposed for 1 hour to carbon particles (250 $\mu g/m^3$, MMAD 1 μm) or H_2SO_4 (100 $\mu g/m^3$) alone, or H_2SO_4-coated carbon black particles (100 $\mu g/m^3$ of H_2SO_4), with intermittent exercise. Electron microscopy findings suggest successful coating of the particles. Group data did not show any symptomatic or respiratory functional changes of any exposure on healthy and asthmatic subjects. However, one asthmatic subject showed severe clinical manifestations and substantial decrements in $FEV_{1.0}$ and FVC following carbon and acid treatments. Acid-coated carbon particles induced much greater adverse health responses than did acid or carbon black alone in this asthmatic subject, who might represent a vulnerable subgroup.

A few recent animal toxicological studies provide new insights for the nature of reactive components of particulate matter. As will be discussed in the next section, studies with "real-world" particles with surface complexed iron (Tepper and Lehmann, 1994), ultrafine Teflon particles (MMAD <0.06 μm) (Oberdorster *et al.*, 1995), or H_2SO_4-coated ultrafine metallic particles (Amdur and Chen, 1989; Chen *et al.*, 1992b) provide interesting models linking a specific component of real-world particulate matter with frank inflammatory effects and acute mortality and morbidity in animals. Metal fume fever (Gordon and Fine, 1993) and polymer fume fever (Shusterman, 1993) have long been recognized as occupationally acquired illnesses that occur as the result of work place exposure to ultrafine metal oxide particles and Teflon particles. Therefore, such models may eventually uncover mechanisms by which particles alone

or complexed with metals could provoke pulmonary inflammation, non-cardiogenic pulmonary airflow obstruction, edema, or exacerbation of arrhythmia.

3.1.2.3. Summary of clinical studies

The main purpose for performing human clinical studies is to evaluate the biological plausibility of adverse health effects of PM observed in epidemiological investigations. Available clinical study data indicate that, although the ranges of acid aerosol concentrations usually exceed those experienced by the general population, only mild decrements in pulmonary function have been induced in asthmatics, a susceptible subgroup. Elderly subjects and the subjects with COPD do not appear to be at higher risk to acid aerosol-induced impairment in pulmonary function than are younger subjects, even when doing mild exercise. No specific link between exposure to less acidic particles and the adverse health effects has been identified. No biochemical and physiological alterations in the cardiovascular system during controlled exposure have been reported.

These clinical observations cannot explain the changes of daily mortality and morbidity following the fluctuation of ambient particle levels that have been observed in epidemiological studies. Possible explanations for the discrepancy between clinical and epidemiological data may lie in as follows: (i) the experimental subjects can only be exposed to the tested air pollutants for short periods for practical and ethical reasons, while an urban pollution episode usually lasts a few days for general population exposure; a clinical study has shown that doubling the length of exposure to H_2SO_4 exerted greater effect on bronchial mucociliary clearance than did an order of magnitude increase in the concentration of H_2SO_4 (Spektor *et al.*, 1989); (ii) the pulmonary function indices that are most often used in clinical studies may not be sensitive enough to indicate particle-induced adverse health effects; (iii) pure aerosols and not atmospheric particles are given subjects in exposure chambers, which may not reflect the possible synergestic effects of PM and aerosol mixtures; (iv) in most human studies, the sizes of aerosols used were above 0.5 μm. Since nanometre-sized ultrafine particles have been found in animal studies to induce acute pulmonary inflammation and death at very low concentrations, and they are present

in ambient air (Brand *et al.,* 1992), ultrafine particles may, as suggested by Seaton *et al.* (1995), be "able to provoke alveolar inflammation, with release of mediators capable, in susceptible individuals, of causing exacerbations of lung disease and of increasing blood coagulability, thus also explaining the observed increases in cardiovascular deaths associated with urban pollution episodes". Currently, such mechanisms remain highly hypothetical.

3.1.3. Toxicological data

The ambient particulate-associated adverse health effects discerned from epidemiology would be greatly strengthened by the existence of plausible, underlying biological mechanisms. Obtaining these mechanisms becomes the purview of toxicology, which can serve to provide mechanistic links between exposure to ambient particle pollution and increased human morbidity and mortality.

Three animal experiments have provided toxicological evidence for adverse health effects from "real world" polluted air. When rats were exposed for 6 months to the ambient atmosphere of Sâo Paulo, Brazil, they demonstrated bronchial secretory-cell hyperplasia, increased mucus secretion, and decreased mucociliary function, which were not observed in rats exposed to cleaner rural air (Saldiva *et al.,* 1992; Lemos *et al.,* 1994). Mice exposed to Los Angeles ambient outdoor air for 43 days showed hyperplasia and hypertrophy of Type II pulmonary cells and the increase of alveolar wall thickness, compared to animals exposed to the cleaner air of Santa Barbara, which may be an indication of early lung injury (Sherwin and Richters, 1991). While these studies may indicate that chronic exposure to "real" ambient air can result in pulmonary effects, the role of particles in producing these responses cannot be determined.

3.1.3.1. Non-acidic particles

Although epidemiological studies have provided evidence indicating the association of increased human morbidity and mortality with ambient particle and $SO_4^=$ levels, animal studies using near neutral $SO_4^=$ generally show very low toxicity. With respect to mortality, exposure to

$(NH_4)_2SO_4$ at 1000-2000 mg/m^3 for 3 days did not cause death in rats (Pepelko *et al.*, 1980).

In the case of morbidity, high concentrations of $SO_4^=$ particles are needed, often in the mg/m^3 range, far beyond current ambient environmental levels. Warren *et al.* (1986) exposed rats to 5.0 mg/m^3 of ammonium sulphate for 2 days, and did not identify any alteration in pulmonary lavage protein content. Wolff *et al.* (1990) exposed rats to diesel exhaust or carbon black without organic compounds adsorbed, at 10 mg/m^3 for 12 weeks, and found mild inflammation in the lungs, as evidenced by increases in numbers of neutrophils and the protein content in bronchoalveolar lavage fluids.

A recent study conducted by a team of Canadian scientists (Bouthillier *et al.*, 1996) has demonstrated that exposure of rats to 50 mg/m^3 of urban particles (MMD 1.4 μm) via nose-only inhalation for 4 hours did not increase levels of protein, fibronectin and alkaline phosphatase in broncho-alveolar lavage fluid, nor did it increase neutrophil counts in broncho-alveolar lavage fluid. However, acute exposure to 50 mg/m^3 of urban particles decreased the secretion of tumour necrosis factor-α and the lipopolysaccharide-stimulated nitric oxide production by alveolar macrophages, and thus to some extent impaired the bactericidal function. Exposure to urban particles for 3 consecutive days resulted in a reduction of alveolar macrophage count (Bouthillier *et al.*, 1996). The exposure concentration of particles in this study was very high in comparison with the ambient PM levels. Nevertheless, when taking into account the lower minute ventilation rate (200 ml/min in rats vs 15 litre/min in humans), lower deposition efficiency (6% for rats vs 35% for humans), shorter term of exposure (4 hours for rats vs 24 hours for humans), and different breathing fashions (nose-only for rats vs nose and mouth for humans) for rats, the authors believed that the lower end of the estimated range of internal deposition level for rats (40 μg/m^2 alveolar surface) was close to the upper end of the estimated range for human pulmonary deposition levels (50 μg/m^2 alveolar surface) when exposed to 50 μg/m^3 of PM.

Another comparative dosimetric study for PM was conducted by Miller *et al.* (1995). Their findings indicate that, while deposition of particles on a mass per unit alveolar surface area is not different between humans and rats, dose metrics based upon particle number per various anatomical parametres (ventilatory unit, alveolus, or alveolar macrophage) exhibit some striking

differences between rats and humans, particularly for particles 0.1-0.3 μm in size. Based on the calculations per ventilatory unit or per alveolus, humans receive much more numbers of particles than do rats when exposed to the same concentration of PM. The trend of differences between humans and rats is even more pronounced for the individuals with compromised lungs compared with normal subjets (Miller *et al.*, 1995). Therefore, rats exposed to 1000 to 1500 $\mu g/m^3$ of particles may actually have received the levles of particles equalent to 120-150 $\mu g/m^3$, the PM level for the Canadian Air Quality Objectives.

In an early investigation, Amdur *et al.* (1978) reported that the irritant potency of $(NH_4)_2SO_4$ for guinea pigs was 10-fold lower than that of H_2SO_4 at the same concentration and aerosol size (500 - 1000 $\mu g/m^3$, MMAD 0.13 - 0.3 μm). Interestingly, while NH_4HSO_4 is more acidic than $(NH_4)_2SO_4$, it was 3-fold less potent than $(NH_4)_2SO_4$ in irritating airways (Amdur *et al.*, 1978).

Sodium sulphite (Na_2SO_3, pH 9) is a stable compound which accounts for approximately 10-30% of the total suspended sulphur oxide aerosols (Chen *et al.*, 1987). When guinea pigs were exposed to aerosols of Na_2SO_3 at 474 - 972 $\mu g/m^3$ (MMAD 0.36 μm) for 1 hour, a dose-related decrease in lung function and increase in wet lung weight were noted (Chen *et al.*, 1987). The authors concluded that the irritant potency of Na_2SO_3 was approximately 10 fold less than H_2SO_4, similar to $(NH_4)_2SO_4$, and 3 to 4 fold higher than NH_4HSO_4 at the same concentration and aerosol size. Another study using beagle dogs demonstrates that chronic inhalation of Na_2SO_3 at a concentration equivalent to 600 $\mu g/m^3$ of SO_2 for 290 days resulted in epithelial proliferation, loss of secretory material and moderate mononuclear cell infiltration in nasal cavity of beagle dog (Takenaka *et al.*, 1994).

Mechanisms of toxicity - The mechanisms of non-acidic particle toxicity can be classified as alteration of alveolar macrophage functions, alteration of inflammatory mediator production, and interaction with cellular macromolecules.

Kleinman *et al.* (1995) exposed rats for 8 weeks to $(NH_4)_2SO_4$ (70 $\mu g/m^3$, 0.2 μm) or ammonium nitrate (350 $\mu g/m^3$, 0.6 μm), two major constituents of the fine particulate matter.

The exposure resulted in a decrease in alveolar macrophage function and moderate morphological alterations of alveolar space. The data indicate that prolonged exposure may enhance $(NH_4)_2SO_4$ toxicity.

Nadeau *et al.* conducted a series of *in vitro* studies (Nadeau *et al.*, 1995a; Nadeau *et al.* 1995b) using human and rat alveolar macrophages obtained by lung lavage. Although low dose of urban particles (up to 100 μg) induced an oxidative burst (Nadeau *et al.*, 1995a), the major effect was the suppression of phagocytosis of rat alveolar macrophages. More significantly, pre-exposure of human or rat macrophages to urban particles suppressed respiratory burst upon secondary challenge with zymosan, a stimulus (Nadeau *et al.*, 1995b). This reveals an impairment of bactericidal function.

When comparing the relative potency of sulphate aerosols in altering alveolar macrophage functions, Schlesinger e*t al.* (1990a) investigated the effects of exposure to H_2SO_4 and NH_4HSO_4, using the phagocytic activity of alveolar macrophages as the endpoint. The exposure of rabbits for 1 hour/day for 5 days to H_2SO_4 at ≥ 1000 μg/m^3 and to NH_4HSO_4 at ≥ 4000 μg/m^3 significantly reduced the phagocytosis of alveolar macrophages. While *in vivo* exposure to a given level of $SO_4^=$ species resulted in greater response to H_2SO_4 than to NH_4HSO_4, macrophages incubated *in vitro* in acidic environment responded similarly regardless of the sulphate species used to adjust the pH, suggesting that the toxic response to sulphate aerosols is more likely due to H^+, rather than to $SO_4^=$. Schlesinger and Chen (1994) have further reported that higher potency of H_2SO_4 than NH_4HSO_4 is likely attributable to higher availability of H^+ from H_2SO_4 than from NH_4HSO_4, because the latter is more readily neutralized by airway ammonia.

Non-acidic particles have been found to alter the release of inflammatory mediators. Devlin *et al.* (1995) incubated human alveolar macrophages with non-lethal concentrations of silica (0-100 μg/ml) or titanium dioxide, a relative innocuous dust (5-50 μg/ml), for 3 or 24 hours *in vitro*. Both silica and titanium dioxide caused substantial release of leukotrienes, and inhibited the production of prostaglandin E_2 and thromboxane.

Interaction of urban particulate matter with cellular macromolecules may occur, leading

to enzyme induction or damage to DNA. The formation of DNA adducts have been observed following incubation of urban particles from Ottawa, Ontario, 10 μg/ml medium, with normal human bronchial epithelial cells for 72 hours (Shah *et al.*, 1995).

Vincent *et al.* (1995) incubated urban particles from Ottawa, Washington, D.C., or St-Louis, or aqueous extracts of $PM_{2.5}$ (100 μg/ml medium) *in vitro* with a panel of HepG2 cell lines transfected with target gene constructs, for 18-24 hours. Urban particles caused gene expression of several enzymes including cytochrome P4501A1, glutathione S-transferaseYa, and a xenobiotic response element, which are biologically critical in chemical biotransformation. The potency of gene induction was correlated with the content of polycyclic aromatic hydrocarbons in particles. The induction of gene expression of cytochrome P4501A1 and the xenobiotic response element was significantly potentiated by co-incubation with rat alveolar macrophages (Goegan *et al.*, 1995), indicating that alveolar macrophages may increase the bioavailability of polycyclic aromatic hydrocarbons from particles.

There are indications that surface-complexed iron on particles is involved in pulmonary injury. To determine potencies of specific metals, Berg *et al.* (1993) examined different fractions of fly ash (12.5-1000 μg/ml, MMAD <4 μm) for their ability to stimulate bovine alveolar macrophages to secrete reactive oxygen species, namely superoxide anion and hydrogen peroxide. They noted that the release of hydrogen peroxide was correlated, in descending order, with the metal contents in the fly ash praticles: iron>manganese>chromium>vanadium>arsenic. The positioning of iron as first in this scheme is consistent with results of some other studies examining the biological effects of iron present as a particle surface coating.

Guilianelli *et al.* (1993) examined the role of iron in PM-related lung injury using chrysotile, nemalite, and hematite particles incubated with rabbit tracheal epithelium *in vitro* (50-100 $\mu g/cm^2$). Surface available iron was correlated both with the oxidizing potency of mineral particles, and with cytotoxicity, and expression of cytokeratin-13 and the formation of cross-linked envelopes of tracheal epithelial cells (two markers of squamous metaplasia), which could be blocked by deferoxiamine, an iron chelator.

A role of particle surface-complexed iron in lung injury is further supported by a study

demonstrating that both the degree of inflammation (indicated by polymorphonuclear leucocytes, eosinophils, lactate dehydrogenase and protein in lung lavage) and bronchoreactivity to acetylcholine were correlated with the Fe^{3+} loading of the particles instilled intratracheally (Costa *et al.,* 1995). Thus, it is possible that reactive oxygen species produced through chemical reactions involving iron could initiate lipid peroxidation of the cell membrane, subsequently resulting in lung injury. pH has been found to play an important role in iron-induced toxicity. Instillation of pure H_2SO_4 at comparable pH induced little inflammatory response, whereas neutralization of fly ash instillate enhanced the toxicity, and resulted in the precipitation of additional particulate material (Costa *et al.,* 1995).

Hence, the results to date suggest that surface-complexed iron on particles has a significant role in the generation of oxidants and the elicitation of lung toxicity.

In addition to iron, other metals may also involve in particle toxicity. Incubation of urban particles from Ottawa, Washington, D.C., or St-Louis, or aqueous extracts of $PM_{2.5}$ (100 μg/ml medium) *in vitro* with a panel of HepG2 cell lines transfected with target gene constructs caused expression of genes for metallothionein and heat shock protein-70 (Vincent *et al.,* 1995). The potency for induction of metal and stress responses was correlated with the content of copper in particles.

Sensitive subpopulations - Epidemiological studies suggest that there may be sensitive subpopulations that are specially susceptible to the adverse effects from inhaled particles. One particular group may be those having lungs compromised by respiratory disease. To investigate the effects of PM exposure on those susceptible subgroups, a number of experiments with animal models have been carried out. Rabbe et al. (1994) exposed rats with elastase-induced emphysema to two particle atmospheres, a California-type aerosol [consisting of particles of graphitic carbon, natural clay, NH_4HSO_4, $(NH_4)_2SO_4$, NH_4NO_3, $PbSO_4$, $VOSO_4$, $MnSO_4$, and $NiSO_4$, MMAD 1.1-1.5 μm], and an London-type aerosol [consisting of NH_4HSO_4, $(NH_4)_2SO_4$, coal fly ash, and lamp black carbon, MMAD 0.8-0.9 μm]. While a 3-day exposure (23 hours/day) to the London aerosol produced a significant greater increase in pulmonary DNA and

RNA contents in emphysema rats than in normal rats, there were no changes in tracheobronchial clearance or lung permeability compared to normals. A 30-day exposure to the California aerosol enhanced small airway lesions in emphysema rats, but did not alter lung hydroxyproline, tracheobronchial clearance, or small airway fibrosis.

In another study using young rats with elastase-induced emphysema, a 24-month exposure (7 hours/day, 5 days/week) to whole diesel exhaust (3,500 $\mu g/m^3$) was conducted (Mauderly *et al.*, 1990). At the end of the exposure, pulmonary function, the contents of enzymes, protein and collagen in lung lavage fluid, and histopathological and morphometric endpoints were examined. There was no evidence that the diseased lungs were more susceptible to the diesel exhaust than the normal lungs. However, less soot accumulated in lungs of emphysematous rats than in those of non-emphysematous rats, suggesting that the reduced burden of diesel exhaust in emphysema lungs was due to the differences in deposition and/or clearance compared to normal lungs.

In a recent observation, rats with induced pulmonary hypertension were found to be extremely sensitive to particle inhalation (Costa *et al.*, 1994), which is suggestive of a clue to the increased cardiovascular mortality and morbidity demonstrated in epidemiological studies.

In general, non-acidic particles show very low toxicity in inducing animal mortality and morbidity. High concentrations of PM are needed, often in the mg/m^3 range, to induce toxicity. However, a study of particle exposure dosimetry in rats has provided a fresh viewpoint, implying that animal toxicity data may be relevant to observed associations between ambient PM exposure and human health outcomes. The main mechanism for non-acidic particle-induced toxicity reported lies in the alteration of inflammatory mediator production, alteration of alveolar macrophage functions (often suppression of phagocytosis), and interaction with cellular macromolecules. It appears that the toxicity of PM depends largely on the acidity and size of particles. The evidence that surface-complexed iron and copper on particles can exert substantial inflammatory responses has provided more information in the mechanism by which non-acidic particles could provoke lung injury. However, more information is needed concerning the toxicity of iron-containing particles at ambient levels. The findings on the susceptibility of

diseased animals to particulate pollution are significant, but inconclusive evidence exists. More research is required.

3.1.3.2. Acid aerosols

Similar to ammonium sulphate, fairly high concentrations of H_2SO_4 are required to induce animal acute mortality. Above 4 mg/m^3 of H_2SO_4 is required for acute lethality of guinea pigs, a species that is believed to be the most sensitive. The animal mortality induced by H_2SO_4 is primarily due to laryngeal or bronchoconstriction (Office of Air Quality Planning and Standards *et al.,* 1982).

In the case of H_2SO_4-induced animal morbidity, chronic exposure for up to 1 year at relatively low concentrations (125-250 μg/m^3) has produced a response characterized by hyperplasia of epithelial secretory cells and hypertrophy in small airways (Gearhart and Schlesinger, 1989; Schlesinger *et al.,* 1992c). However the authors did not observe inflammatory response to low concentrations of H_2SO_4 (Gearhart and Schlesinger, 1989; Schlesinger *et al.,* 1992c). The characteristic acute morphologic responses, such as alveolitis, bronchitis and edema, can be produced by H_2SO_4 only at very high concentrations (27 mg/m^3) in highly sensitive guinea pigs (Wolff *et al.,* 1986).

Mechanisms of acid aerosol toxicity - The possible mechnaisms of H_2SO_4 toxicity can be classified as immunosuppression, bronchial hyperreactivity, and alteration of mucociliary movement.

Pulmonary alveolar macrophages play a key role as main cellular defense against pathogenic organisms in specific immunological defense mechanisms. Exposure of rabbits to H_2SO_4 aerosol (75 μg/m^3, 2 hours) has been found to cause a decrease in the amount of reactive oxygen intermediates and the reduction in tumour necrosis factor-α activity that are critical for maintaining pulmonary immunocompetence in pulmonary alveolar macrophages (Zelikoff and Schlesinger, 1992). Repeated inhalation of high concentrations of H_2SO_4 (750 or 1000 μg/m^3, 2 hour/day for 4 days) reduced the ability of rabbit pulmonary alveolar macrophages to uptake and

kill pathogenic bacteria, as well as to suppress the activity/production of tumour necrosis factor-α and interleukin-1α (Zelikoff *et al.*, 1994). These findings indicate that the pulmonary alveolar macrophages can be a potential target for toxic air particles, which may contribute a better understanding concerning the possible mechanisms underlying the association between aerosol acidity and increased incidence of acute bronchitis observed in epidemiological studies.

In order to determine if particle size influences toxic effects of H_2SO_4, Chen *et al.* (1992a) examined the effects of fine (0.3 μm) and ultrafine (0.04 μm) H_2SO_4 aerosols (300 $\mu g/m^3$) on biochemical and cellular parameters of bronchoalveolar lavage fluid from exposed guinea pigs. Four days of exposure (3 hours/day) to fine aerosols enhanced the phagocytic activity of recovered alveolar macrophages, while an identical exposure to ultrafine aerosols depressed phagocytic function. A depression in intracellular pH was noted 24 hours following 4 days of exposure to the ultrafine aerosols, but not the fine aerosols. Thus, acid exposure produced a change in intracellular pH and phagocytic function of the alveolar macrophages, and the effect was particle size-dependent. Since the same mass concentration of H_2SO_4 was used for aerosols of both sizes, ultrafine H_2SO_4 aerosols as a population may have delivered a higher dose to the macrophages than fine H_2SO_4 aerosols. Enhancement of phagocytosis at a low dose and depression of phagocytosis at a higher dose have been reported in macrophages exposed to acidic media *in vitro* (Schlesinger *et al.*, 1990a). Hence, the differences in response between fine and ultrafine aerosols may be attributable, to some extent, to the doses of acid aerosols delivered to macrophages *in vivo*.

Fine H_2SO_4 aerosols have been demonstrated to induce nonspecific airway hyperresponsiveness, a hallmark of human asthma, in otherwise healthy animals. A single 3-hour inhalation of 75 $\mu g/m^3$ of H_2SO_4 aerosols resulted in evidence of rabbit bronchial hyperresponsiveness to acetylcholine and histamine (El-Fawal and Schlesinger, 1994). When rabbits were exposed to 250 $\mu g/m^3$ of H_2SO_4 for 1 hour per day, 5 days per week for 4 months, H_2SO_4 caused bronchial hyperresponsiveness and alterations in airway diameter and secretory cell number, while pulmonary mechanics parameters did not show significant change (Gearhart and Schlesinger, 1989). The underlying mechanism for hyperresponsiveness appears to be

interference with normal contractile/dilatory homeostatic processes in the airways via modulation of airway receptors involved in maintenance of airway tone. This assumption is supported by an observation of decreases in the production of pulmonary prostaglandins E_2 and $F_{2\alpha}$, and thromboxane B_2, by H_2SO_4 inhalation (250-1000 $\mu g/m^3$, 1 hour/day for 5 days) in rabbits (Schlesinger *et al.*, 1990b). These eicosanoids serve as potent mediators of smooth muscle tone and inflammatory response.

Long-term exposure to H_2SO_4 (250 $\mu g/m^3$) for 4 month also resulted in a reduction of mucociliary clearance (Gearhart and Schlesinger, 1989). The slowing of tracheobronchial mucociliary clearance reflects changes in mucus secretory capacity, alteration in the type of mucus produced, and disruption of normal morphology of cilia and ciliated cells, which, again, can lead to the impairment of pulmonary defense capacity (Samet and Cheng, 1994).

Species differences in susceptibility - With respect to species differences, it appears that guinea pigs are more sensitive in response to H_2SO_4 insult. Exposure of guinea pigs to 14 mg/m^3 of H_2SO_4 for 4 hours induced a significant shift in breathing pattern, whereas 4 hours exposure of rats to 100 mg/m^3 did not cause any changes (Bjarnason *et al.*, 1994). Inter-species differences in the effects of H_2SO_4 on alveolar macrophage function were also examined by Schlesinger *et al.* (1992a). Based upon *in vitro* response of alveolar macrophages to acidic challeng, and subsequent effect on phagocytic activity, a ranking of sensitivity in descending order was found to be: guinea pig > rat > rabbit > healthy, nonsmoking human.

Rahman *et al.* (Rahman *et al.*, 1995) compared differences between rat and human alveolar macrophages in producing reactive oxygen species in response to pollution particles. Particles (carbon black, amorphous and crystalline silica, ultrafine titanium dioxide, asbestos) were incubated with alveolar macrophages, and production of superoxide anion and hydroxygen dioxide were measured. Preliminary results suggest that human alveolar macrophages have a more active oxidative burst than rat macrophages, which may render humans more susceptible than rats to inhaled particles.

In summary, very high concentrations of acid aerosols, usually in the range of mg/m^3, are

required to induce animal mortality and acute morphological alterations. Short term exposure to H_2SO_4 aerosol at the concentrations as low as 75 $\mu g/m^3$ can attenuate the release of reactive mediators that are involved in maintaining the reactivity of pulmonary alveolar macrophages. The biological mechanisms of H_2SO_4 are characterized as immunosuppression, bronchial hyperreactivity, and changes in mucociliary movement. There appears to be inter-species differences in terms of sensitivity to H_2SO_4-induced alteration of alveolar macrophage function.

3.1.3.3. Ultrafine Particles

As discussed above, although there have been numerous epidemiological studies relating acute or chronic ambient particulate exposure to increased human morbidity and mortality, toxic responses observed in human clinical and animal toxicological studies occur most often at PM concentrations well above ambient levels. Adverse health effects observed in toxicological studies at ambient particulate levels are minimal.

One explanation for the lack of biological plausibility for the associations identified at ambient particulate level is because of the particle sizes used for animal studies. Some investigations have demonstrated that when the particle size is small enough (MMAD <0.05 μm), even the particles with little intrinsic toxicity can become very toxic. For example, Oberdorster *et al.* (1992) reported that, after intratracheal instillation of fine (>0.2 μm) or ultrafine (~0.02 μm) titanium dioxide (both 500 μg) which is highly insoluble particles of low intrinsic toxicity, ultrafine particles induced substantially more severe acute inflammatory reaction than fine particles, as determined by the increases of protein leakage and numbers of inflammatory cell counts in lung lavage fluid. The inflammatory response by ultrafine particles was dose-dependent at the range of 65 to 500 μg. Concomitantly, the authors found that inhaled ultrafine titanium dioxide translocated into pulmonary interstitium to a greater extent than fine titanium dioxide particles (Oberdorster *et al.*, 1992; Ferin and Oberdorster, 1992), via endocytosis by pulmonary Type I and Type II cells (Ferin *et al.*, 1992; Lehnert *et al.*, 1993), retained in the lung for longer period of time (Lehnert *et al.*, 1993; Oberdorster *et al.*, 1994), and induced more severe pulmonary inflammation (Oberdorster *et al.*, 1994).

A study conducted by Amide *et al.* (1994) using a human tracheobronchial cast and sodium chloride particles also showed a particle size-dependent deposition efficiency. Inspiratory and expiratory deposition efficiency increased substantially with a decrease of particle sizes (0.1 to 0.005 μm). In addition, a correlation between particle surface area and prolonged tissue retention time was noted (Oberdorster *et al.,* 1994), suggesting that larger surface area of ultrafine particles may play a key role in biopersistence and inflammatory responses of these specifically small particles.

While studies using titanium dioxide were carried out mostly for weeks and at high doses (at mg/m^3 range), the effects were not of an acute nature. In another study conducted by the same group of researchers (Oberdorster *et al.,* 1995), rats were exposed to freshly generated thermodegradation products of polytetrafluoroethylene (PTFE) containing singlet ultrafine particles (MMAD 26 nm), at inhaled concentrations of less than 60 $\mu g/m^3$, below the level of the Canadian Ambient Air Quality Objectives for particulate matter (24 hour average 120 $\mu g/m^3$). The short time exposure to PTFE (10-30 minutes) resulted in acute haemorrhagic pulmonary inflammation and death. The acute toxicity and lethality of PTFE apparently were not attributed to vapour phase fluoro compounds, such as hydrogen fluoride, carbonylfluoride, or perfluoroisobutylene, since the amount of these compounds generated at the temperature (415-420°C) used in this study was minimal (Shusterman, 1993), and lung injury by those fluoro compounds was not observed at low concentrations (Oberdorster *et al.,* 1995). The toxicity of PTFE to rats was reduced significantly when the aerosols were allowed to age, presumably due to the process of particle aggregation with time (Oberdorster *et al.,* 1995). Similarly, Warheit *et al.* reported 100% mortality in rats exposed for 30 minutes to 200 $\mu g/m^3$ of fresh ultrafine PTFE aerosols (0.05 μm); mortality decreased to 20% if the aerosols were aged for 5 minutes (Warheit *et al.,* 1990). Analysis of bronchoalveolar lavage fluid and histopathology indicate that the rats died of severe lung injury (Warheit *et al.,* 1990).

The newest data presented by Oberdorster and co-workers have shown concentrations as low as about 9 $\mu g/m^3$ inhaled for 30 minutes causing pulmonary inflammation in rats, along with the up-regulation of several inflammatory mediators including interleukin-6 (Oberdorster, 1995).

The evidence that the surface area of the retained particles in pulmonary interstitium, rather than their mass, correlates best with the inflammatory response (Oberdorster *et al.,* 1994), implies that the induction of mediators (e.g., chemotactic factors, growth factors, enzymes) from macrophages is a function of the particle surface area that interacts with the receptors of alveolar macrophages.

Ultrafine particles are constantly generated from combustion processes and from gas-to-particle conversion, and the ambient levels can exceed the concentrations used in the above animal studies (Brand *et al.,* 1992). Therefore, the ultrafine particle model has provided an explanation for the increased acute and chronic mortality and morbidity observed in sensitive subpopulation during episodes of elevated air pollution. However, very little information is available with regard to the exposure of general population to ambient levels of ultrafine particulate matter.

While most toxic effects of acid aerosols observed in animal studies are at concentrations well above peak ambient levels of 50 to 75 $\mu g/m^3$ (Spengler *et al.,* 1989), a series of studies have demonstrated that coating of ultrafine metal oxide particles with H_2SO_4 can significantly enhance the potency of H_2SO_4 at much lower concentrations. Amdur and Chen exposed guinea pigs to 20 $\mu g/m^3$ of H_2SO_4 coated on ultrafine zinc oxide particles (MMAD 0.05 μm, 2.5 mg/m^3), either 1 hour single time, or 3 hours daily for 5 days (Amdur and Chen, 1989). Single exposure produced bronchial hypersensitivity to acetylcholine, whereas repeated exposure resulted in inflammatory responses of the guinea pig airways and decrements in lung volumes and pulmonary diffusion capacity (Amdur and Chen, 1989). A single 1-hour exposure to 30 $\mu g/m^3$ of H_2SO_4-coated ultrafine zinc oxide particles also caused significant increase in pulmonary resistance of guinea pigs (Chen *et al.,* 1992b). A ten-fold higher concentration of pure ultrafine H_2SO_4 aerosol (MMAD 0.06 μm) alone was required to produce similar effects (Chen *et al.,* 1992b). The same concentration of zinc oxide particles without the acid coating did not produce such effects (Amdur and Chen, 1989; Chen *et al.,* 1992b). These studies suggest that ultrafine particles can potentiate the toxicity of H_2SO_4 synergistically. Another observation by Chen *et al.* (1991) indicates that single or multiple exposure to 24 $\mu g/m^3$ of H_2SO_4 layered on the ultrafine zinc

particles sensitized guinea pigs to subsequent H_2SO_4 or ozone (0.15 ppm) exposure, resulting in further reduction of lung volumes and diffusing capacity.

There is evidence that ultrafine H_2SO_4 aerosols (0.04 μm) result in greater depressions in both intracellular pH and phagocytic function of alveolar macrophages than do fine H_2SO_4 aerosols (0.27 μm) (Chen *et al.*, 1992a). H_2SO_4-coated ultrafine zinc oxide particles can initiate changes in production of prostaglandin $F_{2\alpha}$ and leukotriene B_4 (Chen *et al.*, 1989), which are involved in mediating the tension of bronchial smooth muscle and inflammatory responses, and may thus constitute a mechanism of ambient acidic PM-induced adverse health effects.

3.1.3.4. Interaction of particulate matter with other air pollutants

Ambient air pollution is composed of a complex mixture of particles and gases, and therefore potential synergistic interactions among various pollutants should be considered. The 1990 acid aerosol assessment report reviewed the evidence for the interaction between acid aerosols and ozone, and concluded that the evidence for synergism was equivocal. Some laboratory studies showed no interaction between ozone and acid aerosols using morphology as an indicator, while others demonstrated a synergistic effect using biochemical and mucus secretion endpoints (Toxic Air Pollution-Health Effects Section, 1990).

Since then, more studies have been carried out, and have indicated that the type of interaction between ambient air pollutants depends on the endpoint and the duration of the exposure. Single exposure of rabbits to low levels of H_2SO_4 aerosol (50-125 $\mu g/m^3$) in conjunction with ozone (0.1-0.6 ppm) for 3 hours showed antagonistic interaction in phagocytic activity of macrophages and superoxide production by stimulated macrophages, while synergistic effect of the pollutants was observed in stimulating tumour necrosis factor activity from macrophages (Schlesinger *et al.*, 1992d) and bronchial hyperreactivity (El-Fawal *et al.*, 1992). Repeated exposure of rabbits to the mixture of H_2SO_4 (75-125 $\mu g/m^3$) and ozone (0.1-0.6 ppm), 3 hours per day for 5 days, induced synergistic/additive interactions in stimulating bronchial hyperresponsiveness and down-regulation of macrophage function (McGovern *et al.*, 1993). In addition, repeated inhalation of mixture of ozone (0.4 ppm), H_2SO_4 (500 $\mu g/m^3$) and carbon

particles (250 $\mu g/m^3$) for 5 days lead to greater lung parenchyma lesion and change in breathing pattern in rats compared with exposure to ozone alone, while there was no synergestic effect on depression of phagocytic activities of macrophages (Kleinman *et al.,* 1993). Long-term exposure of rabbits to the mixture of H_2SO_4 (125 $\mu g/m^3$) and ozone (0.1 ppm) showed an increase in secretory cell number by 4 months, but the response became attenuated with continued exposure (Schlesinger *et al.,* 1992c).

Although non-acidic particles generally reveal minor toxicity to experimental animals, several studies have demonstrated that the injurious responses to ozone can be altered by sulphate aerosols. Warren *et al.* (1986) investigated the interaction between inhalation of $(NH_4)_2SO_4$ and ozone by continuously exposing rats to ozone (0.2 ppm) with and without concurrent exposure to 5 mg/m^3 $(NH_4)_2SO_4$ (0.5 μm) for 2-7 days. A synergistic interaction between ozone and the $(NH_4)_2SO_4$ was identified by more than additive increases in the rate of hydroxyproline synthesis by lung tissue and lavage protein content. In another study, Last *et al.* (1984) reported that repeated exposure to the mixture of ozone (0.64 - 0.96 ppm) and aerosolized $(NH_4)_2SO_4$ (5 mg/m^3, MMAD 1 μm) for 3 days caused significant increases in the numbers of lung macrophages, monocytes and fibroblasts, and the enhancement in collagen synthesis rates, when compared with values obtained from animals exposed to ozone alone. Only relatively minor changes were observed with ammonium sulphate alone. However, a study by Wong *et al.* (Wong *et al.,* 1994) demonstrates that repeated exposure to ozone (0.2 ppm) in combination with inorganic sulphate (65 $\mu g/m^3$), nitrate (365 $\mu g/m^3$) and road dusts (65 $\mu g/m^3$, MMAD 5 μm) for 4 days significantly reduced the abnormal expression of heat shock protein in rat lung induced by exposure to ozone alone.

Recently, a group of Canadian researchers exposed rats to a combination of ozone (0.8 ppm) and Ottawa particles (50 mg/m^3, MMAD 1.4 μm) via nose-only inhalation for 1 or 3 days (Bouthillier *et al.*, 1996). Exposure to PM alone did not increase levels of protein, fibronectin and alkaline phosphatase in broncho-alveolar lavage fluid, nor did it exacerbate these effects of ozone following co-exposure. While ozone or PM alone altered some aspects of alveolar macrophage physiology, these cellular effects appeared to be attenuated by co-exposure of two

pollutants. However, PM potentiated the ozone-induced neutrophilic infiltration in lung lavage.

Therefore, toxicological interaction between PM and ozone appears complex, and requires further investigation.

3.1.4 Summary for particulate matter induced direct adverse health effects and future research directions

Summary

Epidemiological investigations have demonstrated a coherent relationship between ambient particle concentrations and human mortality and morbidity. A similar phenomenon has been observed in several countries with different medical care systems. The epidemiological data appropriately identify the same susceptible populations at greatest risk as would be anticipated clinically. The PM relative risk estimates derived from the recent studies suggest a higher susceptibility indicated for the infants and the elderly, and for those with pre-existing compromised respiratory and cardiovascular conditions, who may constitute sensitive subpopulations to the health effect implications of the exposures to PM pollution. The risk of mortality and morbidity increases with PM pollution levels, often with a near linear dose-response fashion, without obvious threshold. While there is an indication that aerosol strong acidity may contribute to the associations between PM and human health effects, some studies have shown that aerosol acidity has a threshold in initiating respiratory illness. The key reactive component(s) of PM responsible for the increases in mortality and morbidity remains an open question.

It is noteworthy that co-pollutants, such as SO_2 and ozone, may significantly confound the outcomes for PM due to their co-linearity. Several studies have demonstrated that the effect of PM on daily mortality can be substantially attenuated when SO_2 and ozone are simultaneously included in the regression, and vice versa, due to the statistical correlations among these pollutants. Therefore, new approaches need to be explored. It is possible that these co-pollutants may cause synergistic adverse health effects.

Compared with epidemiological studies, there is some inconsistency observed in human clinical and animal toxicological studies. Although there is no question to the plausibility of a causal relationship between high levels of particle exposures (as high as 4000 $\mu g/m^3$) and excess morbidity, and maybe even mortality, in clinical and animal studies, there remain doubts about such a causal relationship extending to concentrations as low as 50 $\mu g/m^3$. One explanation of such a discrepancy is that in clinical and animal studies, most often sulphate alone, or sulphate plus one or two other pollutants such as ozone, is used, which may not reflect the complexity of ambient particles. Highly reactive chemicals, such as metals and free radicals, which are adsorbed on the surface of "real world" PM, may substantially potentiate the toxicity of particulate matter.

Comparative studies of particle exposure dosimetry in rats and humans have provided a fresh viewpoint. These studies suggest that PM-induced animal toxicity data may be relevant to observed associations between ambient PM exposure and human health outcomes, when taking into consideration the differences of airway geometry, minute ventilation rate, deposition efficiency, exposure term, and breathing fashion, between animals and humans.

Other explanations may lie in the short exposure duration and insensitive indices (such as lung function) that are used in controlled human clinical studies.

Recent toxicological investigations using ultrafine particles (MMAD <0.06 μm), "real-world" particles with surface-complexed iron, and H_2SO_4-coated ultrafine metallic particles, have provided new insights for the nature of reactive components of PM. These studies have offered interesting models linking a specific component of real-world PM at low concentrations with frank immunological responses and inflammatory effects, and acute mortality and morbidity, in animals.

Future research directions

(1). A research agenda should be developed and implemented as a basis to characterize physical-chemical properties of ambient ultrafine particles and their episodic fluctuation associated with specific meteorological conditions. Reliable instrumentation needs to be

developed to quantify ultrafine aerosol in ambient air.

(2) Attention should be given to the human health effects induced by ambient ultrafine particles, iron-containing particles, and acid-coated ultrafine metallic particles, through human clinical study and epidemiological investigation.

(3) More sensitive biological markers of tissue injury should be introduced to link low PM exposure levels with the adverse health effects, in order to enhance the sensitivity of human clinical studies.

(4) In order to identify subpopulations sensitive to the fluctuation of ambient PM pollution, an effort should be made to investigate the susceptibility of cardiovascular system-compromised patients (such as patients with chronic congestive heart failure) in controlled clinical studies, since there is epidemiological evidence of increased cardiac mortality and morbidity with the increase in PM levels. The relation between air pollution and blood coagulation tendency requires further investigation.

(5) Epidemiological analyses should be conducted on air pollution data obtained from representative areas with unique air pollution patterns, such as St. John, New Brunswick with high aerosol acidity but low PM levels, as well as other regions with just the opposite situation, high PM but low acid like Los Angeles, in order to elucidate the potential key reactive component(s) of PM responsible for the increases in mortality and morbidity.

(6) Personal monitoring should be carried out, in order to determine exactly what and when the elderly and susceptable populations are exposed, indoor and outdoor.

3.2. Sulphur dioxide

SO_2 is water soluble, and is readily absorbed from the moist surfaces of the upper respiratory tract. Human clinical studies have demonstrated that in resting conditions, inhaled SO_2 gas is almost completely (80% - 90%) removed by nasal absorbtion (Speizer and Frank, 1966). However, persons breathing orally at rest would receive a higher lung exposure to SO_2

(Kirkpatric *et al.*, 1982; Speizer and Frank, 1966). Fine particles, especially hygroscopic salts such as sulphate which adsorbs SO_2 in inhaled air, may also increase the penetration of SO_2 to the lower respiratory tract.

3.2.1. Epidemiological data

The current Canadian Ambient Air Quality Objectives for SO_2 are 0.9 mg/m^3 for 1-hour average concentration, 0.3 mg/m^3 for 24-hour average concentration, and 0.06 mg/m^3 for annual arithmetic mean (Mellon *et al.*, 1986).

In epidemiological studies, the outcomes examined for an association between ambient SO_2 levels and human health outcomes are very different (Table 3.2.1)(see end of chapter). Several recent investigations have shown that there exists a positive association of daily variations of SO_2 with daily mortality rates of respiratory and cardiovascular diseases (Spix *et al.*, 1993; Xu *et al.*, 1994; Li and Roth, 1995; Moolgavkar *et al.* 1995a), hospital admissions for asthma (Walters *et al.*, 1994) and other respiratory diseases (Sunyer *et al.*, 1991; Ponka and Virtanen, 1994), and the daily diary report of respiratory symptoms (Schwartz *et al.*, 1994), at the annual average concentrations of SO_2 between 0.039 and 0.102 mg/m^3, even when the autocorrelation effect of seasonal and meterological factors and the interactions among air pollutants were controlled using various statistical models.

Spix *et al.* (1993) conducted a daily mortality study in Erfurt, a heavily polluted coal-burning area in East Germany, with daily mean SO_2 levels up to 4,000 μg/m^3 during 1980-1989. They found that for an increase in SO_2 daily mean from 23 to 929 μg/m^3, daily mortality increased by 10%, without apparent threshold. On the other hand, in the Harvard Six-City study of diaries kept by parents of children's respiratory and other illness, there was an apparent threshold for relative odds of low respiratory symptoms at approximately 20 ppb (52.4 μg/m^3) of SO_2 (Schwartz *et al.*, 1994).

A study in Norway assessed the relationship between air quality and the health effects on children (aged 7-13 years) living in a valley containing a SO_2-emitting aluminium smelter (Soyseth *et al.*, 1995). The median exposures to SO_2 and fluoride were 37 μg/m^3 and 4.4 μg/m^3

at ages 0-12 months, and 38 $\mu g/m^3$ and 4.4 $\mu g/m^3$ at 13-36 months. The authors reported that exposure to SO_2 at concentrations below 40 $\mu g/m^3$ during infancy had an increased risk of bronchial hyperresponsiveness. The odds ratio for a 10 $\mu g/m^3$ increase in SO_2 exposure at 0-12 months was 1.62 [95% confidence interval (CI) 1.11-2.35]. The exposure to fluoride was also associated with an increased risk of hyperresponsiveness. The concentrations of other pollutants were not mentioned.

In a very recent study conducted in Canada (Burnett *et al.*, 1995), hospital admissions for respiratory diseases during April 1, 1981 to December 31, 1991, were investigated for 16 cities across Canada. Daily ozone, SO_2, NO_2, CO, and soiling index (COH, correlated with airborne particles) were recorded. After controlling for seasonal patterns, day of the week, and other copollutants, SO_2 pollution (mean 4.7 ppb, 95% percentile 17 ppb) was found to be associated with respiratory hospital admissions.

These results suggest that SO_2 concentrations lower than those given as guidelines in many countries may still produce significant health effects, especially for sensitive subpopulations such as asthmatics and young children.

Other studies investigating the genetic toxicity or carcinogenicity of SO_2 have suggested that exposure to SO_2 (0.334 to 1.20 mg/m^3) in occupational settings may result in an increased frequency of chromosomal aberrations (Meng and Zhang, 1990), although the concentrations of other pollutants in the factory were not reported. An ecological study by Gorham et al. (1989) examined the levels of ambient air SO_2 and the coefficient of haze (an index of small particles producing visual haze in 400 nanometre wavelength light) in 20 Canadian cities, and their relation to age-adjusted breast and colon cancer mortality rates encompassing these cities. Positive associations were observed between the pollution of SO_2 and the coefficient of haze and the mortality rates for colon cancer in men and women, and for breast cancer in women. The authors proposed that the elevated mortality rates for colon and breast cancers may be attributed to the ability of SO_2 and aerosols to block transmission of vitamin D-producing ultraviolet sunlight.

Data from other studies argue that SO_2 may not be a significant predictor for health

effects. In a prospective cohort study, Abbey *et al.* (1995b) followed 6,340 nonsmoking California Seventh-Day Adventists since 1977 for incidence of cancer and myocardial infarction, and development or increasing severity of respiratory diseases. No statistically significant associations were found between any of the disease outcomes studied and ambient air SO_2 concentrations. Another study investigating the effects of air pollution on respiratory health of more than 1,000 children living in four nonindustrial communities of the Netherlands also did not find any association between SO_2 at the level of 0.0149 mg/m^3 in winter and respiratory symptoms and the alteration of pulmonary function (Hoek and Brunekreef, 1994). Similarly, another prospective cohort study by Dockery *et al.* demonstrated that there was a very weak association between mortality rate and SO_2, while respirable particles showed strong association with mortality rates (Dockery *et al.*, 1993a). There appears to be a threshold for relative risk of mortality at approximately 10 ppb (26.2 μg/m^3) of SO_2 (Dockery *et al.*, 1993a).

In Canada, a cross-sectional investigation was conducted to compare air pollution in 10 rural communities and the effects on childhood respiratory health (Stern *et al.*, 1994). While SO_2 levels were far below the Canadian Ambient Air Quality Objectives in all the communities (annual mean 0.4 to 2.0 ppb, or 1.0 to 5.5 μg/m^3), there were still observable decrements of lung function of children in association with increased ambient levels of ozone and $SO_4^=$ particles, further suggesting that SO_2 may not be the major damaging agent in these communities.

The discrepancy between these studies may possibly lie in the differences in the populations selected (sensitive versus non-sensitive), or the ecological nature of some of these studies (namely key confounding variables are not necessarily measured). However, it should be noted that people spend a majority of their time indoors, and hence personal exposure is usually dominated by indoor exposure. It has been reported that the mean concentration of SO_2 in the personal total and indoor samples can be 5-fold lower than the concentration outdoors (Brauer *et al.*, 1989), due to the quick deposition of the gas on indoor surfaces. In the case of sensitive individuals, such as patients with respiratory and cardiovascular diseases, since they would be expected to spend more time indoors than do healthy individuals, the contribution of SO_2 to personal exposures would therefore be further reduced. On the other hand, the indoor

concentrations of $SO_4^=$ and NH_4^+ have been found similar to those measured outdoors (Brauer *et al.*, 1989; Suh *et al.*, 1993), which may confound the outcomes. Thus, the differences in the population composition and in personal daily activities, when not controlled, may lead to potential biases and variable conclusions.

In addition, different results may also be related to the selection of statistical models. It has been reported that the significance of a pollutant predictor of daily mortality changes from model to model (Li and Roth, 1995; Kinney *et al.*, 1995). For example, recent analyses assessing the association of particulate matter, SO_2 and/or ozone pollution with daily mortality in Steubenville (Moolgavkar *et al.*, 1995b) and Philadelphia (Moolgavkar *et al.*, 1995a; Li and Roth, 1995), U.S., have demonstrated that the effect of particulate matter on daily mortality was substantially attenuated when SO_2 and ozone were simultaneously included in the regression, and vice versa, due to the correlations among these pollutants. As reported by Li and Roth (1995), each of the models has its strengths and weaknesses, and therefore, new approaches that include multiple pollutants and other covariates need to be explored.

3.2.2. Clinical data

Although there is no evidence of SO_2 toxicity in animal studies at the low concentrations encountered in ambient air, a few clinical studies have suggested that significant changes in pulmonary airway resistance may occur, at a concentration of 0.68 mg/m^3 or lower, in sensitive subjects such as asthmatics, during mild to moderate exercise (Sheppard *et al.*, 1982; Kirkpatric *et al.*, 1982; Linn *et al.*, 1987; Heath *et al.*, 1994). To asthmatics or other individuals with already compromised pulmonary function, relatively small increases in airway resistance are of greater clinical significance than they are to "healthier" individuals.

Interactions of SO_2 with other pollutants have been examined in clinical studies. Pre-exposure to 0.12 ppm of ozone increased the sensitivity of asthmatic patients to SO_2, so that concentrations as low as 0.262 mg/m^3 caused bronchoconstriction during moderate exercise (Koenig *et al.*, 1990). Pre-exposure to NO_2 (0.3 ppm), on the other hand, had no effect on the airway response to SO_2 in asthmatic patients (Rubenstein *et al.*, 1990).

3.2.3. Toxicological data

The toxicological effects of acute, subacute and chronic SO_2 exposure in animals have been well documented and have provided some evidence for the mechanism(s) of SO_2 toxicity.

Most studies conducted in recent years are at concentrations far in excess of those normally encountered in ambient air. Exposure to 0.815 to 4.077 mg/m^3 of SO_2 *in vitro* for 30 to 120 minutes initiated the release of reactive oxygen-intermediates, which are the inducers of inflammatory cell accumulation, from pulmonary alveolar macrophages and peripheral blood mononuclear cells (Kienast *et al.*, 1994a). Exposure to 2.60 to 100.0 mg/m^3 of SO_2 *in vitro* caused an impairment of mucociliary activity and ultrastructural alterations of guinea pig airways (Knorst *et al.*, 1994; Riechelmann *et al.*, 1995) and human airway ciliated cells (Kienast *et al.*, 1994b). Acute exposure to SO_2 at concentrations between 1.0 to 9.0 mg/m^3 for 5 min caused an increased resistance of rabbit lung (Islam and Schlipkoter, 1990). Co-administration of SO_2 with sodium chloride droplets resulted in greater effects on lung function (Koenig *et al.*, 1983), which suggests that acidity rather than SO_2 may be the critical factor. At concentrations of SO_2 lower than 0.16 mg/m^3, no toxic effects in animals have been observed.

3.2.4. Summary for sulphur dioxide - induced direct adverse health effects

The outcomes from epidemiological studies regarding the associations between ambient SO_2 levels and human health effects are very different. Overall data have shown that the associations of daily SO_2 variations with daily mortality and morbidity rates are weak, and are readily confounded by other pollutants. The differences in the population composition and in personal daily activities among the epidemiological investigations also may lead to different conclusions.

A few clinical studies have suggested that significant changes in pulmonary airway resistance may occur, at a concentration of 0.68 mg/m^3 or lower, in sensitive subjects such as asthmatics. Moreover, there is evidence that pre-exposure to 0.12 ppm of ozone can potentiate

the sensitivity of asthmatic patients to SO_2.

Toxicological studies have shown very low toxicity of SO_2 in inducing animal pulmonary injury. Most toxic effects of SO_2 are observed at concentrations far beyond those normally encountered in ambient air. The main mechanisms observed for SO_2 toxicity lie in initiating the release of reactive oxygen-intermediates from pulmonary alveolar macrophages and peripheral blood mononuclear cells, and impairing mucociliary activity of airway ciliated cells.

Table 3.1.1. Summaries of recently published epidemiological studies relating human mortality to ambient levels of particulate matter

PM Measure (Concentrations)	Study Description	Results and Comments	References
BS[a] (mean = 90.1 $\mu g/m^3$, 24-h average daily max. = 709 $\mu g/m^3$)	Daily total mortality was analyzed for associations with BS, SO_2, and H_2SO_4 in London, England, during 1963-1972 winters. Mean daily temperature and relative humidity also were considered.	PM, SO_2 and H_2SO_4 were all indicated as having significant associations with mortality (0, 1 day lag). The log of H_2SO_4 concentrations was more strongly associated with raw total mortality in bivariate analyses than is BS or SO_2. Temperature also was correlated (negatively) with mortality, but with a 2-day lag. Seasonality was addressed by studying only winters and by applying a high-pass filter to the series and analyzing residuals.	Thurston *et al.*, 1989
BS	Daily total mortality in Athens, Greece, and surrounding boroughs during 1975-1987 was related to BS, SO_2, NO_2, O_3 and CO_2 using multiple regression.	The daily number of deaths was positively and statistically significantly associated with all pollutants, but the association was strongest with BS.	Katsouyanni *et al.*, 1990a
BS (annual mean range =	Mortality was studied for the period 1975-1982 in	Mortality was generally higher on high SO_2	Katsouyanni *et*

51.6 to 73.3 $\mu g/m^3$, max. daily = 790 $\mu g/m^3$)	athens, Greece. One hundred and ninety nine days with high SO_2 (>150 $\mu g/m^3$) were each matched on temperature, year, season, day of week, and holidays with two low SO_2 days.	days, with the difference being most pronounced for respiratory conditions. Mortality by-cause comparisons was made between groups by analysis of variance by randomized blocks. BS levels for each group was not provided. BS was correlated with SO_2 at r = 0.73, but was not directly employed in the analysis. BS-SO_2 confounding was not addressed, limiting interpretability of results.	*al.*, 1990b
KM[b] (mean = 25; SD = 11)	Shumway *et al.* 's 1970-1979 Los Angeles mortality dataset was analyzed using a high-pass filter to allow investigation of short-wave (acute) associations with environmental variables (by removing seasonality effects). Environmental variables were considered in regression analyses included temperature, relative humidity, extinction coefficient, KM, SO_2, NO_2, CO and O_3.	Analyses demonstrated significant associations between short-term variations in total mortality and pollution, after controlling for temperature. Day-of-week effects were found not to affect the relationships. The results demonstrated significant mortality associations with O_3 lagged 1 day, and with temperature, NO_2, CO and KM. The latter three pollutants were highly correlated with each other, making it impossible to separately estimate particulate matter associations with mortality from motor vehicle related pollutant effects on	Kinney and Ozkaynak, 1991

		daily mortality.	
TSP (mean = 87 $\mu g/m^3$; 24-h average range: 5% to 95% tiles = 46 to 137 $\mu g/m^3$,)	Total deaths in Detroit, MI, 1973-1982 were analyzed using Poisson methods. Environmental variables considered included TSP, SO_2, O_3, temperature, and dew point. Seasonality was controlled via multiple dummy weather and time variables.	Significant associations were reported between TSP and mortality in autoregressive Poisson models (RR^c of 100 $\mu g/m^3$ TSP = 1.06). However, most TSP data were estimated from visibility, which is best correlated with the fine aerosol (and especially sulphate) portion of the TSP. Thus, results suggest a fine particle association.	Schwartz, 1991
TSP (mean = 77 $\mu g/m^3$; max. = 380 $\mu g/m^3$; 5% to 95% tiles = 37 to 132 $\mu g/m^3$)	Total- and cause-specific daily mortality in Philadelphia, PA during 1973-1980 was related to daily TSP and SO_2 (n = 2,700 days). No other pollutants were considered in the analysis. Poisson regression models, using GEE methods, included controls for year, season, temperature, and humidity. Autocorrelation was addressed via autoregressive terms in model.	Strongest associations were found with pollution on the same and prior days. Total mortality (mean = 48/day) was estimated to increase 7% (95% C.I. = 4 to 10%) for a 100 $\mu g/m^3$ increase in TSP. Cause-specific effects of TSP were larger for COPD (+19%), pneumonia (+11%), and cardiovascular disease (+10%). People ≥65 years had higher relative risk than younger people. SO_2 associations were non-significant in simultaneous models with TSP, but correlations of their coefficients were not	Schwartz and Dockery, 1992a

		reported.	
TSP (mean = 111 $\mu g/m^3$; 24-h average range: 10% to 90% tiles = 36 to 209 $\mu g/m^3$)	Daily total mortality in Steubenville, OH, between 1974-1984 was related to TSP, SO_2, temperature, and dew point. Poisson regression was employed, because of very low death counts/day (mean = 3.1). Regressions were controlled for season by including dummy variables for winter and spring, and autoregressive methods also were used to address any remaining autocorrelation.	In regressions controlling for season and weather, previous day's TSP was a significant predictor of daily mortality. SO_2 was less significant in regressions, becoming nonsignificant when entered simultaneously with TSP. Autoregressive models gave similar results.	Schwartz and Dockery, 1992b
PM_{10} (mean = 47 $\mu g/m^3$; 24-h max. = 365 $\mu g/m^3$; 5 day max. = 297 $\mu g/m^3$)	Total, respiratory, and cardiovascular mortality in Utah County, UT, during 1985-1989 was related to 5-day moving average PM_{10}, temperature, and humidity. Time trend and a random year terms also were included in autoregressive Poisson models employed. Seasonality was not directly addressed in this basic model, but the addition of four seasonal dummy variables changed results little.	A significant positive association between total non-accidental mortality and PM_{10} was observed, the strongest association being with the 5-day moving average of PM_{10}. The association was largest for respiratory disease, the next largest for cardiovascular, and the lowest for all others. Association was noted below 150 $\mu g/m^3$ of PM_{10}. The possible influence of other pollutants was discussed, but not directly addressed.	Pope *et al.*, 1992
PM_{10}	Total mortality in St. Louis, MO, and	Statistically significant daily mortality	Dockery *et al.*,

(St. Louis, MO: mean = 28 $\mu g/m^3$; 24-h max. = 97 $\mu g/m^3$; Kingston/Harriman, TN: mean = 30 $\mu g/m^3$; 24-h max. = 67 $\mu g/m^3$)	Kingston/Harriman, TN (and surrounding counties), during September 1985 to August 1986 was related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temperature, dew point, and season using autoregressive Poisson models.	associations were found with PM_{10} and $PM_{2.5}$ in St. Louis, but not with other pollutants. In Kingston/Harriman, PM_{10} and $PM_{2.5}$ approached significance, while other pollutants did not. Seasonality was reduced by season indicator, variables, but within season long wave cycles was not directly addressed. H^+ was not as important in associations with daily mortality as the mass concentrations of particles.	1992
BS (range = 50 to 250 $\mu g/m^3$)	Daily total mortality in Athens, Greece, during July, 1987 (when a major "heat wave" occurred) was compared to the deaths in July during the previous 6 years. Environmental variables considered included: temperature, discomfort index, BS, and SO_2. Confounding effects of day-of-week, month, and long-term trends were addressed via dummy variables in OLS regression models.	Mean daily temperature above 30°C was found to be significantly associated with mortality. The main effects of all air pollutants were not significant, but the interaction between high air pollution and temperature were significant for SO_2 and suggestive ($p< 0.20$) for ozone and BS.	Katsouyanni *et al.*, 1993
SP[d] (range = 10 to 650 $\mu g/m^3$)	Daily total mortality in Erfurt, East Germany, during 1980-1989 (median = 6/day) was related to SO_2, SP, temperature, relative humidity, and precipitation. SP	Both SO_2 and SP were found to be significantly associated with increased mortality. In a simultaneous regression, SP	Spix *et al.*, 1993

	measurements were made only 1988-1989. Autoregressive Poisson models employed (due to low deaths/day) also included indicator variables for extreme temperatures and adjustments for trend, season, and influenza epidemics.	remained significant while SO_2 did not. Correlations of these coefficients were not provided, however. Pollution effect size was similar to that for meteorology.	
PM_{10} (mean = 48 $\mu g/m^3$; 24-h max. = 163 $\mu g/m^3$)	Total daily mortality in Birmingham, AL, from August 1985 to December 1988 was related to PM_{10}, temperature, and dew point. Poisson models employed addressed seasonal long wave influences by the inclusion of 24 sine and cosine terms having periods ranging from 1 month to 2 years. Autoregressive linear models also were applied.	Significant associations were found between total mortality and prior day's PM_{10}. Various models gave similar results, as did eliminating all days with $PM_{10} > 150$ $\mu g/m^3$. However, the possible role of other pollutants was not evaluated.	Schwartz, 1993
BS (mean = 90.1 $\mu g/m^3$; range = 0 to 350 $\mu g/m^3$)	Further analysis of London, England data (1965-1972) was examined by Thurston et al. (1989). Spectral and advanced time series methods was applied, including pre-whitening and autoregressive moving average methods. Environmental variables considered included BS, SO_2, H_2SO_4, temperature, and relative humidity.	Estimated pollution mean effect was 2 to 7% of all London winter deaths (mean = 281/day). However, the various pollutants' effects could not be separated. Independent model test on the 1962 episode confirmed the appropriateness of such methods. Long-wave was addressed by considering winters only and by pre-whitening the data.	Ito *et al.*, 1993

BS (mean = 83 $\mu g/m^3$; range = 18 to 358 $\mu g/m^3$)	Daily total mortality in Athens, Greece, during 1984-1988 (mean =38/day) was related to BS, SO_2, CO, temperature, and relative humidity. Autoregressive OLS models employed also included indicator variables for season, day of week, and year.	BS, SO_2, and CO were all found to be individually significantly associated with increased mortality. In simultaneous regressions, the size of all coefficients declined, with SO_2 still significant and BS approaching significance. CO was no longer significant, but was highly correlated with BS (r = 0.74) in the data.	Touloumi *et al.*, 1994
TSP (mean = 52 $\mu g/m^3$; SD = 19.6 $\mu g/m^3$)	Daily total and cause-specific mortality in Cincinnati, OH, (mean total = 21/day) during 1977-1982 was related to TSP, temperature, and dew point. Poisson model was employed with dummy variables for each month and for eight (unspecified) categories of temperature and dew point. Linear and quadratic time trend terms also were included. Spline and nonparametric models also were applied. Autocorrelation was not directly addressed.	TSP was significantly associated with increased risk of total mortality. RR was higher for the elderly and for those dying of pneumonia and cardiovascular diseases. However, the analysis failed to consider other pollutants, and there remains the potential for within-month, long-wave confoundings.	Schwartz, 1994d
TSP (mean = 375 $\mu g/m^3$, max. = 1003 $\mu g/m^3$)	Daily deaths during 1989 in two residential areas in Beijing, China, (mean total = 21.6/day) was related to TSP and SO_2 using Poisson methods. Controlling indicator variables for quintiles of temperature and	Significant mortality associations were found for ln (SO_2) and ln (TSP). Associations were strongest for chronic respiratory diseases. In simultaneous regressions, SO_2 was significant,	Xu *et al.*, 1994

	humidity, as well as for Sunday also were included. Long-wave confounding and autocorrelation were not directly addressed. However, season-specific results presented.	but not TSP. However, the two pollutants were highly correlated with each other (r = 0.6), as well as with temperature. In season-specific analyses, both pollutants were significant in summer, but only SO_2 in winter.	
PM_{10} (mean = 82.4 $\mu g/m^3$; 24-h average SE = 38.9 $\mu g/m^3$)	Total mortality among the elderly (≥ 65 years old) (mean = 63/day) in São Paulo, Brazil during May 1990 through April 1991 was related to two day average of PM_{10}, SO_2, NO_x, O_3, CO, temperature, humidity, and day of week. Season was addressed by including seasonal and monthly dummy variables. Temperature was addressed using three discrete dummy variables.	Significant associations were found between total elderly deaths and all pollutants considered. In a simultaneous regression, PM_{10} was the only pollutant which remained significant. The PM_{10} coefficient actually increased in this regression, suggesting interpollutant interactions. Correlations of the pollutant coefficients were not provided.	Saldiva *et al.*, 1994
PM_{10} (mean = 40 $\mu g/m^3$; 24-h max. = 96 $\mu g/m^3$)	Total, cardiovascular, cancer, and respiratory mortality in Toronto, Canada, during 1972-1990 was related to PM_{10}, TSP, $SO_4^=$, CO, O_3 temperature and relative humidity. Nineteen-day moving average filtered data were used in OLS regressions. Sixty-three hundred and three PM_{10} values were estimated based on TSP, $SO_4^=$, COH, visibility and temperature data, using model developed from 200 PM_{10} sampling	After controlling for weather and long wave influences, significant associations were found between all pollutants considered and mortality. However, it was not possible to separate the PM_{10} association from other particulate measures considered ($PM_{2.5}$, TSP and COH). Simultaneous PM and O_3 regressions gave significant coefficients for	Ozkaynak *et al.*, 1995

	days during the period.	each.	
TSP (mean = 69 $\mu g/m^3$; 5% to 95% tiles = 32 to 120 $\mu g/m^3$)	Age and cause-specific daily mortality in Philadelphia, PA during 1973 and 1990 was related to daily TSP, SO_2, and O_3. Other environmental variables included were: temperature, barometric pressure, humidity, and precipitation. Various models were employed, including Poisson and autoregressive. Prefiltering methods also were applied to remove long-waves in data.	TSP effect was found only in winter season. TSP was not significant in by-cause analyses of those <15 or ≥65 years of age. TSP effects were weakened by the addition of other pollutants (TSP-SO_2 r = 0.57). However, the inclusion of barometric pressure and precipitation in these models may have acted as surrogates for PM, potentially confounding results. Correlations between TSP and these variables were not presented.	Li and Roth, 1995
TSP (spring mean = 67 $\mu g/m^3$, min. to max. = 16.5 - 338 $\mu g/m^3$; summer mean = 74 $\mu g/m^3$, min. to max. = 21.0 - 210 $\mu g/m^3$; fall mean = 64.9 $\mu g/m^3$, min. to max. = 14.5 - 215 $\mu g/m^3$; winter mean = 66.3 $\mu g/m^3$, min. to max. = 19.3 - 205 $\mu g/m^3$)	Daily total mortality in Philadelphia during 1973-1988 was investigated, and related to TSP, SO_2, ozone. Poisson regression and nonparametric bootstrap and bias-corrected accelerated bootstrap confidence intervals were used. Both methods yielded similar results. The effects of weather were controlled by analyzing mortality separately for each season and including both pollution variables and quintiles of temperature in the regression models simultaneously.	When all three pollution covariates and weather were considered simultaneously in the regression model, TSP was not significantly associated with mortality in any season. Ozone was associated with mortality in summer (RR = 1.15, 95% CI = 1.07-1.24), while SO_2 was associated with mortality in spring (RR1.19, 95% CI = 1.06-1.33), fall (RR = 1.14, 95% CI = 1.00-1.29) and winter (RR = 1.21, 95% CI = 1.09-1.35). The pollutant	Moolgavkar *et al.*, 1995a

		covariates were highly correlated.	
TSP (mean = 113 $\mu g/m^3$; 10% to 90% tiles = 38 to 212 $\mu g/m^3$)	Daily mortality in Steubenville, OH during 1974-1984 was related to TSP, SO_2, temperature, and dew-point (to allow comparisons of results with Schwartz and Dockery, 1992b). Poisson method was employed. Analyses were done overall and by-season.	In single pollutant models, the TSP coefficient was the same as Schwartz and Dockery (1992b), but TSP effects were found to be attenuated by SO_2 inclusion in the model. SO_2 was also attenuated by the addition of TSP. It is concluded that TSP and SO_2 effects cannot be separated in this dataset. Intercorrelations among these variables were not presented.	Moolgavkar *et al.*, 1995b
PM_{10} (mean = 58 $\mu g/m^3$; 24-h max. = 177 $\mu g/m^3$)	Total mortality in Los Angeles, CA, during 1985-1990 were related to PM_{10}, O_3, CO, temperature, and relative humidity. Poisson models employed addressed seasonal long-wave influences by including multiple sine and cosine terms ranging from 1 month to 2 years in periodicity. OLS and long linear models also were tested. Winter and summer were analyzed separately also.	Association between PM_{10} and mortality was found to be only mildly sensitive to modelling method. CO also was individually significant. The addition of either CO or O_3 lowered the significance of PM_{10} in model somewhat, but the PM_{10} coefficient was not as affected, indicating minimal effects on the PM_{10} association by other pollutants in this case.	Kinney *et al.*, 1995
PM_{10} (mean = 38 $\mu g/m^3$, 24-h max. =128 $\mu g/m^3$)	Total mortality in Los Agneles, CA and Chicago, IL during 1985-1990 was related to PM_{10}, O_3, and temperature. Analysis focused on importance of	Average of multiple sites' PM_{10} was found to be significantly associated with mortality in each city after controlling for season,	Ito *et al.*, 1995

	monitor choice to modelling results. Poisson models used addressed seasonal long wave influences by including multiple sine/cosine terms ranging from 1 month to 2 years in periodicity.	temperature and O_3. Other pollutants and relative humidity were not considered. Individual sites' PM_{10} varied from non-significant to strongly significant. Also, dividing the data by season diminished the significance of the multi-site average PM_{10} in mortality regressions. Both site selection and sample size were concluded to influence results.	
PM_{10} (mean = 115 $\mu g/m^3$; 24-h max. =367 $\mu g/m^3$)	Total, respiratory, and cardiovascular daily deaths/day (means = 55, 8, and 18, respectively) in Santiago, Chili during 1989-1991 were related to PM_{10}, O_3, SO_2, NO_2, temperature and humidity. Seasonal influences were addressed by various methods, including seasonal stratification, the inclusion of sine/cosine terms for 2.4, 3, 4, 6, and 12 month periods, prefiltering, and the use of a nonparametric fit of temperature. Log of PM_{10} was modeled using OLS with first order autoregressive terms.	Significant association was found between PM_{10} and daily mortality, even after addressing potential confounders (e.g., weather), other pollutants, lag structure, and outliers. Strongest associations were found for respiratory deaths. SO_2 and NO_2 also were significantly associated individually, but only PM_{10} remained significant when all were added simultaneously to the regression. Correlations of the coefficients were not reported.	Ostro *et al.*, 1995
PM_{10}	Total, respiratory, circulatory, and cancer mortality	Average and single site PM_{10} were significant	Styer *et al.*, 1995

(Cook County median = 37 $\mu g/m^3$; max. = 365 $\mu g/m^3$; Salt Lake County median = 35 $\mu g/m^3$; max. = 487 $\mu g/m^3$)	were studied in Cook County, 1985-1990. Elderly, total by race and sex also were evaluated. Poisson regression with seasonal adjustments, meteorological variables, and pollen was tested. In Salt Lake County, total and elderly mortality. One daily station in Cook County and two daily monitoring stations in Salt Lake County, plus multiple stations, were used.	predictions of PM_{10} in Cook County for total, elderly, cancer, and elderly white mortality, but marginal for respiratory, circulatory, and elderly black. PM_{10} was significantly associated with fall and spring mortality, but not with summer or winter mortality. No significant effects were found in Salt Lake County. No copollutants were reported.	
PM_{10} (variable by month and year)	Reanalysis of Utah County mortality, 1985-1990, was conducted. Data were broken down by year, season cause and place of death. PM_{10} was entered as dichotomous variable, less or greater than 50 $\mu g/m^3$. No adjustment was made for copollutants or for weather in Poisson regression, except for daily minimum temperature. Poisson regression was employed without GEE.	Variations in RR did not appear to be associated with high or low PM_{10} days. High RR was found for cancer deaths, age < 10 years, at home. Highest RR was in spring. There was an increased RR for sudden infant death syndrome. Patterns appear noncausal.	Lyon *et al.*, 1995
BS	Reanalysis of daily mortality in Greater London (1965-1972) was conducted by season, temperature range, and ambient BS, H^+ and SO_2 concentrations. In each season, the majority of days fell within one or two temperature ranges, within which the daily death	Regression analyses showed strong associations between daily mortality and the daily logs of the concentrations of H^+ and SO_2. The association with BS was weaker. However, the intercorrelations between	Lippmann and Ito, 1995

	rates also fell within narrow ranges.	copollutants were not addressed.	
TSP (mean = 77.6-82.7 $\mu g/m^3$) $SO_4^=$ (mean = 11.1 $\mu g/m^3$) Fine particles (mean = 23 $\mu g/m^3$) Inhalable particles (mean = 37.8-50.9 $\mu g/m^3$)	A cross-sectional study was conducted to analyze 1980 U.S. vital statistics and the ambient concentrations of TSP, $SO_4^=$, fine particles, and inhalable particles. Multiple regression analyses were used.	$SO_4^=$ was consistently found to be a significant predictor of total mortality. Fine particle mass coefficients were often found to be significant in the mortality regressions. TSP and inhalable particles were not significant. Other potential confounders (occupation, sex, smoking, O_3, SO_2, etc.) were not addressed.	Ozkaynak and Thurston, 1987

[a]BS, British smoke.

[b]KM, carbonaceous particulate matter, a measure of particulate optical reflectance.

[c]RR, relative risk.[d]SP, suspended particles, a generic term for total suspended particles.

Table 3.1.2. Summaries of recently published epidemiological studies relating human daily hospital admissions to ambient levels of particulate matter

PM Measure (Concentrations)	Study Description	Results and Comments	References
$SO_4^=$ (mean of the hourly max.: May - October = 3.34 - 3.80 $\mu g/m^3$; November - April = 2.88 - 3.78 $\mu g/m^3$) Coefficient of haze (COH) (mean of the hourly max.: May - October = 0.319 - 0.368; November - April = 0.410 - 0.475)	Attendances at the emergency departments of 9 acute care hospitals in Vancouver region from July 1, 1984 to October 31, 1986, were recorded. Daily temperature, SO_2, NO_2, $SO_4^=$, COH and ozone were mornitored. Pearson correlation coefficients were calculated between asthma visits and pollution variables on the same day and lagged 24 and 48 hr, separately for the periods May-October, and November-April.	There was little variation in pollution variables for each day of the week. There was a significant variation in emergency room visits by day of the week. In summer, in 1-14 age group, asthma visits were correlated with $SO_4^=$ levels on lagged 24 hr. In 15-60 age group, total respiratory visits and asthma visits were significantly correlated to $SO_4^=$ levels on the same day and lagged 24 hr. In ≥61 age group, $SO_4^=$ levels on lagged 24 and 48 hr were correlated with asthma visits and respiratory visits. Ozone levels were correlated with total visits, but not with respriatory and asthma visits. In winter, $SO_4^=$ levels on lagged 24 and 48 hr were correlated with asthma and respiratory visits only in ≥61 age group. SO_2 levels in summer and winter were also	Bates *et al.*, 1990

		correlated with respirtory visits.	
Black smoke (yearly mean 24-hr average = 72.9 $\mu g/m^3$; range 39-310 $\mu g/m^3$)	Emergency room admissions for chronic obstructive pulmonary disease (COPD) in Barcelona, Spain, during 1985-1986, were assessed. Black smoke, SO_2, CO, NO_2, and O_3 were measured. Autocorrelation was controlled by transfer function modelling for 2-day lag minimum temperature, season, day of week and 1-day lag wind velocity. Autoregressive linear regression analysis was used.	SO_2, black smoke, CO, and NO_2 were intercorrelated. After adjusting for meteorologic and temporal variables, daily emergency room admissions for chronic obstructive pulmonary disease increased by 0.02 and 0.01 for 1 $\mu g/m^3$ of SO_2 and black smoke, respectively, and 0.11 for 1 mg/m^3 of CO.	Sunyer *et al.*, 1991
TSP, $SO_4^=$, and COH (coefficient of haze, a measure of fine black carbon particles)	Daily respiratory admissions in Southern Ontario (1979-1985) was related to TSP, $SO_4^=$, COH, SO_2, and O_3. Stepwise multiple regression was used to examine the joint effects of copollutants and weather variables.	Weak but statistically significant associations were found between respiratory hospital admissions and $SO_4^=$, SO_2 and O_3.	Lipfert and Hammerstrom, 1992
$SO_4^=$ (mean = 6.9-9.3 $\mu g/m^3$, maximum = 26-42 $\mu g/m^3$)	Daily respiratory hospital admissions in Buffalo, Albany and New York City, New York, during 1988-1989, were related to $SO_4^=$, H^+, O_3 and temperature during June - August, 1988-1989. Hospital admissions and environmental data were first detrended to eliminated long-wave autocorrelations.	$SO_4^=$, H^+, and O_3 were significantly associated with total respiratory and asthma admissions on the same day and/or on subsequent days in Buffalo and New york City, especially in 1988. Same-day bi-variate analysis showed high intercorrelations among copollutants. No	Thurston *et al.*, 1992

	Day-of-week effects were removed via regression. Least squares regressions were conducted of daily admissions on temperature and pollution.	simultaneous regression was done with multi-pollutants. O_3 showed the highest mean effects estimates, while H^+ had the highest RR estimates.	
PM10 (mean = 29.6 $\mu g/m^3$; SD = 18 $\mu g/m^3$; min. and max. range = 6-103 $\mu g/m^3$)	Daily records of asthma emergency room visits were compiled from 8 hospitals in the Seattle area during September 1, 1989 through September 30, 1990. Daily PM_{10}, SO_2, and ozone were monitored. Poisson regressions were used and weather, season, time trends, age, hospital, and day of the week were controlled.	The daily counts of emergency room visits for persons under age 65 were significantly associated with PM_{10} exposure on the previous day. The mean of the previous 4 days' PM_{10} was a better predictor. The relative risk for a 30 $\mu g/m^3$ increase in PM_{10} was 1.12 (95% CI 1.04-1.20).	Schwartz *et al.*, 1993
Black smoke	Daily emergency room admissions for COPD in Barcelona, Spain, during 1985-1989, were assessed. Black smoke and SO_2 were measured. Separate analyses were performed for winter and summer. Autoregressive linear regression analysis was used, and minimum temperature, a dummy variable for Monday, and a dummy variable for the year 1987 were included in the model. Ridge regressions were used to isolate the association between each air pollutant and COPD emergencies, and to remove the	The collinearity correlation coefficient between SO_2 and black smoke was 0.7. For SO_2, an increase of 25 $\mu g/m^3$ produced adjusted changes of 6% and 9% in emergency admission for COPD in winter and summer, respective. For black smoke, a similar change was found in winter, but the change was smaller in summer.	Sunyer *et al.*, 1993

	influence of multicollinearity.		
$SO_4^=$ (mean = 3.1-8.2 $\mu g/m^3$)	Daily respiratory hospital admissions in Ontario, Canada, were analyzed for association with $SO_4^=$. Ozone was measured. Linear regression was used on filtered data to control temperature changes. 1-day lag generated best correlation.	Positive associations were found between respiratory admission and both O_3 and $SO_4^=$. O_3 accounted for 5.2% of additional respiratory admissions, and $SO_4^=$ accounted for 1% of excess respiratory admissions during May - August. Largest impact was seen on infants. Other pollutants were not in the model.	Burnett *et al.*, 1994
TSP (mean = 62-87 $\mu g/m^3$) PM_{10} (mean = 30-39 $\mu g/m^3$) $PM_{2.5}$ (mean = 16-22 $\mu g/m^3$) $SO_4^=$ (mean = 38-124 $nmol/m^3$)	Daily respiratory admissions in Toronto, Canada, were analyzed. Co-pollutants (O_3, SO_2, NO_2, H^+) were measured. Simultaneous linear regression (included O_3 and H^+ or $SO_4^=$, or $PM_{2.5}$, or PM_{10}, or TSP) was used on filtered data. The effect of temperature was addressed.	Simultaneous regression showed that strongest associations were with O_3 and H^+; somewhat weaker with $SO_4^=$. No associations were found with SO_2 and NO_2. Intercorrelations between copollutants except O_3 were not addressed.	Thurston *et al.*, 1994
PM_{10} (mean = 36 $\mu g/m^3$, 10% to 90% tiles = 18-58 $\mu g/m^3$)	Respiratory hospital admissions of patients aged 65 y and older in Minneapolis-St. Paul, Minnesota, during 1986-1989 were analyzed. Daily air pollution data	An increase of 100 $\mu g/m^3$ in daily PM_{10} had a RR = 1.17 (95% CI = 1.33-1.02) for pneumonia admissions, and a RR = 1.57 (95%	Schwartz, 1994b

	included O_3 and PM_{10}. Poisson regression analysis was used to control for time trend, seasonal fluctuations, and weather.	CI =2.06-1.20) for COPD admissions. An increase of 50 ppb in daily O_3 had RR = 1.15 (95% CI = 1.36-0.97) for pneumonia admission.	
PM_{10} (mean = 45 $\mu g/m^3$, 10% to 90% tiles = 19-77 $\mu g/m^3$)	Respiratory hospital admissions of patients aged 65 y and older in Birmingham, Alabama, during 1986-1989 were analyzed. Daily air pollution data included O_3 and PM_{10}. Poisson regression analysis was used to control for time trend, seasonal fluctuations, and weather.	An increase of 100 $\mu g/m^3$ in daily PM_{10} had a RR = 1.19 (95% CI = 1.07-1.32) for pneumonia admissions, and a RR = 1.277 (95% CI =1.08-1.50) for COPD admissions. An increase of 50 ppb in daily O_3 with 2-day lag had RR = 1.14 (95% CI = 0.94-1.38) for pneumonia admission, and a RR= 1.17 (95% CI = 0.86-1.60) for 1-day lag COPD admissions.	Schwartz, 1994c
PM_{10} (May to October, 24-hr mean = 29.5 $\mu g/m^3$; July and August, 24-hr mean = 31.5 $\mu g/m^3$) $SO_4^=$ (May to October, 24-hr	Daily urgent respiratory admissions were related with PM_{10}, $SO_4^=$, and O_3 in Montreal, Canada, between 1984-1988. A high-pass filter was used to eliminate yearly seasonal trends in the data. Two time periods (May to October, and July through August) were examined separately. Pearson's R correlations were calculated between admission data and exposure levels on the same day and 1-4 day s prior to the day	Asthma admissions in May-October periods increased by 2.7% over mean levels for each 12 $\mu g/m^3$ increase in PM_{10} 3-d prior to the admission. In July -August periods, respiratory non-asthma admissions increased by 9.6% over mean admission level when $SO_4^=$ was at or above 8.2 $\mu g/m^3$ (its 90th percentile) 4-d prior to the admission day.	Delfino *et al.*, 1994

mean = 4.2 $\mu g/m^3$; July and August 24-hr mean = 4.9 $\mu g/m^3$)	of admission. Co-regressions of O_3 and PM were done. Autocorrelation was examined through lag 15 days.		
$SO_4^=$ (April to September, 24-hr mean = 3.0-7.7 $\mu g/m^3$; October to March 24-hr mean = 2.0-4.7 $\mu g/m^3$)	Daily cardiac and respiratory admissions to 168 acute care hospitals in Ontario, Canada, were related with $SO_4^=$ and O_3 during 1983-1988. A 19-day linear filter was used to eliminate yearly seasonal trends in the data. Two time periods (April to September, and October to March) were examined separately. Rates were adjusted for day-of-the-week effects and variation in admissions between hospitals. Pearson's R correlations were calculated between admission data and exposure levels on the same day and 1-3 day s prior to the day of admission. Co-regressions of O_3 and PM were done.	A 13 $\mu g/m^3$ increase in $SO_4^=$ recorded on the day prior to admission was associated with a 3.7% increase in respiratory admissions and a 2.8% increase in cardiac admissions. Admissions for cardiac diseases increased 2.5% for those under 65 years and 3.5% for those 65 years and older. After adjusting for ambient temperature and O_3, increases in respiratory admissions were 3.2% for April to September, and 2.8% for October to March; increases in cardiac admissions were 3.4% for April to September, and 3.4% for October to March.	Burnett *et al.*, 1995
Soiling index (COH)	Hospital admissions for respiratory diseases during April 1, 1981 to December 31, 1991, were investigated for 16 cities across Canada. Daily ozone, SO2, NO2, CO, and soiling index (COH) were recorded. COH is correlated with airborne particles.	All the environmental variables were positively associated with respiratory hospitalizations.	Burnett *et al.*, 1995

	The multivariate random effects relative risk regression model was used to relate the environmental variables to the daily respiratory admissions. A 19-day weighted moving regression filter was employed to remove seasonal patterns from the data.		
PM_{10} (mean in New Haven = 41 $\mu g/m^3$; 10% to 90% tiles = 19 to 67 $\mu g/m^3$; mean in Tacoma = 37 $\mu g/m^3$; 10% to 90% tiles = 14 to 67 $\mu g/m^3$)	Daily counts of hospital admissions for respiratory diseases were constructed for persons aged ≥65 years in New Haven, Connecticut, and Tacoma, Washington, during January 1, 1988 to December 31, 1990. Daily SO_2, PM_{10} and ozone were monitored. Daily respiratory admission counts were regressed on temperature, humidity, day of the week, and air pollutants. A 19 day weighted moving regression filter was used to remove all seasonal and subseasonal patterns from the data. Each pollutant was first examined individually and then multiple pollutant models were fitted.	PM_{10} levels were associated with respiratory hospital admissions of the elderly (RR = 1.06 with 95% CI 1.00-1.13 in New Haven, and 1.10 with 95% CI 1.03-1.17 in Tacoma, for a 50 $\mu g/m^3$ increase in PM_{10}). The PM_{10} associations were little changed by controlling for ozone or SO_2. Levels of SO_2 and ozone were also associated with respiratory admission independently.	Schwartz, 1995
PM_{10} (mean = 48 $\mu g/m^3$; 10% to 90% tiles = 22 to 82 $\mu g/m^3$)	The associations between air pollution and daily cardiovascular hospital admissions for elderly patients (aged 65 years and older) were examined in Detroit, Michigan, 1986-1989. PM_{10}, O_3, SO_2, CO	After controlling for seasonal and other long-term temporal trends, temperature, and dew point temperature, PM_{10} was associated with daily admissions for ischemic heart disease	Schwartz and morris, 1995

	and weather data were monitored. Dummy variables for each of the 48 months and each day of the week, in the study period, were used to control seasonal and weather variations in illness rates. A linear and quadratic time term was included to capture the long-term temporal trends in hospitalization rates. Autoregression was tested by examining the previous days' admissions, up to a lag of 3 days. Poisson regression was employed to test the association. Two-pollutant regression was tested to determine the independent contributions.	(RR=1.018, 95% CI 1.005-1.032 for an increase of PM_{10} 32 $\mu g/m^3$) and with heart failure admissions (RR=1.024, 95% CI 1.004-1.044). SO_2, CO and O_3 made no independent contribution to ischemic heart disease admissions. CO also showed an independent association with heart failure admission (RR=1.022, 95% CI 1.010-1.034 for a 1.28 ppm increase in CO).	

Table 3.1.3. Summaries of recently published epidemiological studies relating human respiratory symptoms to ambient levels of particulate matter

PM Measure (Concentrations)	Study Description	Results and Comments	References
PM_{10} (yearly mean 24-hr average = 46 $\mu g/m^3$; range = 11-195 $\mu g/m^3$)	Upper and lower respiratory symptoms and medication use of healthy grades 5 and 6 students and asthmatics of 8-72 yr of age were examined, in Utah Valley. PM_{10}, H^+, SO_2, NO_2, and O_3 were measured. Fixed effects logistic regression was used for the relation between same day PM_{10} levels and symptoms and medication use, and for controlling low temperature.	H^+, SO_2, NO_2, and O_3 were well below the standards. Elevated levels of PM_{10} were associated with increases in reported symptoms of respiratory disease and use of asthma medication. Little or no strong particle acidity was present.	Pope *et al.*, 1991
TSP (yearly median = 17-56 $\mu g/m^3$; 10% tiles = 5-34 $\mu g/m^3$, and 90% tiles = 41-118 $\mu g/m^3$)	Children's croup symptoms and obstructive bronchitis in 5 German cities were examined. Daily TSP, SO_2, and NO_2 were monitored. Autoregressive Poisson regression using GEE was applied to examine the joint effects of copollutants and weather variables. One and two days lag between exposure and response was studied.	An increase in TSP levels from 10 $\mu g/m^3$ to 70 $\mu g/m^3$ was associated with a 27% increase in cases of croup; the same increase in NO_2 levels resulted in a 28% increase in cases of croup. No pollutant was associated with daily cases of obstructive bronchitis. Symptoms were predominantly found in 1-2 years of age.	Schwartz *et al.*, 1991
$PM_{2.5}$ (mean = 21.97 $\mu g/m^3$, range	A panel of 207 asthmatics were studied for the recorded respiratory symptoms and frequency of	Airborne H^+ was significantly associated with cough and shortness of breath of asthmatic	Ostro *et al.*, 1991

= 0.51-73.08 $\mu g/m^3$)	medication use, in Denver, in the winter of 1987-1988. Daily $PM_{2.5}$, H^+, $SO_4^=$, HNO_3, and nitrates were monitored. Autoregressive logistic regression was used to analyze which air pollutants were associated with health outcomes. Minimum daily temperature, daily use of a gas stove, day of survey, and day of week were included in the regression. Autocorrelation was corrected.	patients. Cough was also associated with $PM_{2.5}$, and shortness of breath with $SO_4^=$. HNO_3 and nitrates were not significantly associated with respiratory symptoms.	
PM_{10} (mean = 76 $\mu g/m^3$, range = 7-251 $\mu g/m^3$)	Symptomatic and asymptomatic school children of grades 5 and 6 were assessed for upper and lower respiratory symptoms and cough during the winter of 1990-1991, in Utah Valley. PM_{10}, SO_2, and H^+ were monitored. Autoregressive logistic regression using GEE was applied to analyze the association of respiratory symptoms with PM_{10} and low temperature.	Associations between the incidence of respiratory symptoms, especially cough, and PM_{10} pollution were observed for both symptomatic and asymptomatic children. The association was strongest for the symptomatic sample. Respiratory symptoms were more closely associated with 5-day moving-average PM_{10} levels than with concurrent-day levels. The association was also observed at PM_{10} levels below the 24-hr standard of 150 $\mu g/m^3$.	Pope and Dockery, 1992
TSP (rural area mean = 35-40 $\mu g/m^3$; suburbs mean = 40-	A diary study of 625 Swiss children aged 0-5 y was conducted in two cities in Switzerland during 1985-1986. Incidence and duration of symptom episodes	The 6-week average TSP was significantly associated with incidence of coughing episodes, and marginally significant as a	Braun-Fahrlander *et al.*, 1992

45 $\mu g/m^3$; cities mean = 50-55 $\mu g/m^3$)	were examined separately. Daily air pollution data included TSP, SO_2, NO_2 and O_3 in Switzerland. Logistic regression analysis was used to control for time trend, seasonal fluctuations, and weather.	predictor of upper respiratory episodes. NO_2 measured outdoors but not indoors was associated with the duration of all symptoms. TSP was a more significant predictor of duration of all symptoms than NO_2.	
COH (mean = 12 per 100 ft, range = 4-26 per 100 ft) $SO_4^=$ (mean = 8 $\mu g/m^3$, range = 2-37 $\mu g/m^3$)	Daily incidence of upper and lower respiratory symptoms of non-smokers were studied in south California between 1978-1979. $SO_4^=$, coefficient of haze (COH), O_3, SO_2, and NO_2 were monitored. A logistic regression model was used to examine the association between particle pollution and symptoms. Day of study, maximum daily temperature, and a gas stove at home were included in the regression.	A significant association between the incidence of lower respiratory tract symptoms and $SO_4^=$ levels (OR = 1.30, 95% CI 1.09-1.54, for a 10-$\mu g/m^3$ increase), 1-h daily maximum O_3 levels (OR = 1.22, 95% CI 1.11-1.34 for a 10 ppm increase), 7-h average O_3 levels (OR = 1.32, 95% CI 1.14-1.52). No association was found with COH.	Ostro *et al.*, 1993
PM_{10} (6 days above 110 $\mu g/m^3$, 1 day above 150 $\mu g/m^3$)	A diary was used to record acute respiratory symptoms and medication use of children (6-12 years old) with chronic respiratory symptoms, in the winter of 1990-1991, in the Netherlands. PM_{10}, SO_2, NO_2, and black smoke were monitored. Autoregressive logistic regression was used. Autocorrelation was corrected.	There was a consistent positive association between PM_{10}, black smoke, and SO_2 with the prevalence of wheeze and bronchodilator use.	Roemer *et al.*, 1993

PM_{10} (mean = 20.1-28.1 $\mu g/m^3$) $PM_{2.1}$ (mean = 7.3-17.2 $\mu g/m^3$) $SO_4^=$ (mean = 12-67.3 $\mu g/m^3$)	Respiratory symptoms were examined among white children aged 8-12 years from 24 communities in the U.S.A. and Canada. PM_{10}, $PM_{2.1}$, $SO_4^=$, H^+, SO_2, and O_3 were monitored. A two-stage logistic regression model was used. First, a city-specific logistic regression model for the respiratory symptoms was fit to the data, and the adjusted logits were calculated controlling for sex, history of allergies, parental history of asthma, parental education and current smoking in the home. The adjusted logits were then regressed against the city-specific air pollution measurements. The regression coefficients were expressed as odds ratios.	$SO_4^=$ was associated with increased reporting of bronchitis (OR = 1.65, 96% CI 1.12-2.42). Children living in the community with the highest levels of particle strong acidity were significantly more likely to report having had at least one episode of bronchitis in the past year compared to children living in the least polluted community (OR = 1.66, 95% CI 1.11-2.48). No other respiratory symptoms were significantly increased in association with any of the air pollutants of interest. No sensitive subgroups were identified.	Dockery *et al.*, 1993b
PM_{10} (median = 30 $\mu g/m^3$, 10% tile = 30 $\mu g/m^3$, 90% tile =53 $\mu g/m^3$) $PM_{2.5}$ (median = 18 $\mu g/m^3$, 10% tile 7 $\mu g/m^3$, 90% tile = 37	A daily diary of upper and lower respiratory symptoms was collected from the parents of school children in six U.S. cities, between April and August, 1984-1985. PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, $SO_4^=$, and H^+ were monitored. Autoregressive logistic regression using GEE was applied.	A change in 24-h PM_{10} concentration from 20 to 50 $\mu g/m^3$ was associated with a relative odds of 1.53 (95% CI 1.2-1.95) for the incidence of lower respiratory symptoms, a relative odds of 1.22 (95% CI 1.03-1.45) for the incidence of coughing, and a relative odds of 1.22 (95% CI 0.98-1.52) for the incidence of upper respiratory symptoms. There was no	Schwartz *et al.*, 1994

$\mu g/m^3$)		evidence that other measures of particulate pollution were preferable to PM_{10} in predicting incidence of respiratory symptoms. Significant associations were found between SO_2 or O_3 and incidence of coughing, and between SO_2 and incidence of lower respiratory symptoms.	
PM_{10} (mean = 44.9 $\mu g/m^3$; range = 14.1-126.1 $\mu g/m^3$) $SO_4^=$ (mean = 6.7 $\mu g/m^3$; range = 0-29.7 $\mu g/m^3$)	A daily diary of acute respiratory symptoms was collected from 7 to 11-year-old children during three consecutive winters in the Netherlands. PM_{10}, $SO_4^=$, NO_2, SO_2, nitrates, gaseous nitrous acid, and H^+ were monitored. Logistic regression was used. Day of study and minimum temperature were included in the regression models. Pre-whitening was performed to remove autocorrelation. Cross-correlation function was calculated to identify the most relevant lag between air pollution and symptom prevalence.	No association of the measured pollutants with daily incidence and prevalence of acute respiratory symptoms was found. H^+ level was low.	Hoek and Brunekreef, 1994
PM_{10} (annual Ontario mean = 23.0 $\mu g/m^3$, 90% tile = 39.0 $\mu g/m^3$; Saskatchewan mean	In this cross-sectional study, respiratory symptoms and illness history were examined among children from 5 ontario and 5 Saskatchewan communities. PM_{10}. $SO_4^=$, nitrates, O_3, SO_2, and NO_2 were	No significant regional differences were observed in rates of chronic cough or phlegm, persistent wheeze, current asthma, bronchitis in the past year, or any chest illness that kept	Stern *et al.*, 1994

= 18.0 μg/m^3, 90% tile = 37.0 μg/m^3) $SO_4^=$ (annual Ontario mean = 6.6 μg/m^3, 90% tile = 11.5 μg/m^3; Saskatchewan mean = 1.9 μg/m^3, 90% tile = 3.0 μg/m^3)	monitored. Odds ratios were calculated and adjusted for sex, parental smoking, parental education, and gas cooking.	the child at home for 3 or more consecutive days during the previous year.	
PM_{10} (12 hr mean = 35.6 μg/m^3; max. = 83.4 μg/m^3) $PM_{2.5}$ (12 hr mean = 24.5 μg/m^3; max. = 88.1 μg/m^3) Total $SO_4^=$ (12 hr mean = 147.0 nmol/m^3; max. = 515 nmol/m^3) Particle-strong acidity (12 hr mean = 102 nmol/m^3;	The daily presence of cold, cough, or wheeze symptoms of children during the summer of 1990 were recorded in Uniontown, Pennsylvania. Daily SO_2, PM_{10}, $PM_{2.5}$, total $SO_4^=$, particle-strong acidity, ozone and temperature were measured. An autoregressive logistic regression model was used. The covariates included a linear trend parameter, a binary indicator of whether the observation point was in the morning or evening, and the average temperature and pollutant concentration of a single pollutant for the 12-hr monitoring period preceding the diary report with separate pollutant effect	A 12-hr exposure to a 125-nmol/m^3 increase in total $SO_4^=$ was associated with increased cough incidence (OR = 1.64, 95% CI 1.08-2.5). A 12-hr exposure to a 125 nmol/m^3 increment in particle-strong acidity was associated with increased cough incidence (OR = 1.6, 95% CI 1.1-2.4). A 12-hr exposure to a 15 μg/m^3 increase in $PM_{2.5}$ was associated with increased cough incidence (OR = 1.71, 95% CI 1.16-2.5). SO_2 and O_3 had similar effect.	Neas *et al.*, 1995

max. = 676.4 nmol/m^3)	estimates for daytime and overnight exposures.		
Estimates of PM_{10} from TSP mornitored daily	A nonsmoking California Seventh-day Adventist population was followed up between 1977 and 1987 for their development of respiratory symptoms. TSP was mornitored from 1973 to 1987 statewide. Since PM10 was not mornitored statewide before 1985, the concentration was estimated from the levels of TSP. Multivariate statistical models were developed for each of the three diseases-air obstructive disease, chronic bronchitis, and asthma. New cases of disease and persistent prevalence were analyzed by multiple logistic regression models, and changes in symptoms severity score were analyzed by multiple linear regressions.	The RR associated with 1000 hr/year exposure to concentrations of PM_{10} that exceeded 100 μg/m^3 for development of airway obstructive disease was 1.17 (95% CI 1.02-1.33); RR for development of chronic productive cough was 1.21 (95% CI 1.02-1.44); RR for development of asthma was 1.30 (95% CI 0.97-1.73). Stronger associations were observed for those who were exposed occupationally to dusts and fumes. The RR of developing airway obstructive disease as an adult for those who had airway obstructive disease as a child was 1.66 (95% CI 1.15-2.33).	Abbey *et al.*, 1995a
PM_{10} (daily mean = 36-48 μg/m^3; range =11-136 μg/m^3) $SO_4^=$	A daily diary of acute respiratory symptoms was collected from 7 to 11-year-old children during spring and summer of 1989 in the Netherlands. PM_{10}, $SO_4^=$, O_3, NO_2, SO_2, nitrates, gaseous nitrous acid, and H^+ were monitored. Autoregressive logistic regression	No association was found between daily incidence and prevalence of acute respiratory symptoms and same-day or previous day concentrations of the measured pollutants. H^+ level was low.	Hoek and Brunekreef, 1995

(daily mean = 5-7 $\mu g/m^3$; range = 0-27 $\mu g/m^3$)	was used. Cross-correlation function was calculated to identify the most relevant lag between air pollution and symptom prevalence. Pre-whitening was performed to remove autocorrelation.		

Table 3.1.4. Summaries of recently published epidemiological studies relating changes in human pulmonary function to ambient levels of particulate matter

PM Measure (Concentrations)	Study Description	Results and Comments	References
TSP (about one half of the locations in the sample had TSP levels that exceeded 80 $\mu g/m^3$)	A cross-sectional study was designed to investigate the relationship between lung function and quarterly average levels of TSP for adults in 49 of the locations where the First National Health and Nutrition Examination Survey was conducted in the United States. A multivariate regression was conducted including physiological variabels, occupational dust expsoure and TSP against lung function. A graphical technique was used to investigate the shape of the relationship between TSP levels and lung function.	Statistically significant relationships were observed between TSP levels and FVC and $FEV_{1.0}$. An one standard deviation increase (about 34 $\mu g/m^3$) in TSP from the sample mean of 87 $\mu g/m^3$ was associated with an average decrease in FVC of 2.25%. There was an apparent threshold level (approximately 60 $\mu g/m^3$ quarterly average) of TSP below which a relationship with lung function ceases to exist.	Chestnut *et al.*, 1991
PM_{10} (yearly mean 24-hr average = 46 $\mu g/m^3$; range = 11-195 $\mu g/m^3$)	Lung function of healthy grades 5 and 6 students and asthmatics of 8-72 y of age were examined, in Utah Valley. PM_{10}, H^+, SO_2, NO_2, and O_3 were measured. Single period and polynomial-distributed lag models were estimated by regressing ΔPEF on daily PM_{10} levels, low temperature, and a linear time trend	H^+, SO_2, NO_2, and O_3 were well below the standards. Elevated55 PM_{10} levels of 150 $\mu g/m^3$ were associated with a 3-6% decline in PEF. Current day and daily lagged associations between PM_{10} levels and PEF were observed. Little or no strong particle	Pope *et al.*, 1991

	variable. Weighted least-squares regression was used. Autocorrelation was corrected.	acidity was present.	
PM_{10}, $PM_{2.5}$ (indoor and outdoor personal exposure)	Asthmatic and non-asthmatic children recorded the total quantity of time spent in 5 locations in Tucson, Arizona, in a daily dairy. PM_{10}, $PM_{2.5}$ and NO_2 were monitored indoor and outdoor. A daily total personal exposure index was estimated based on estimated or measured concentrations in 5 locations, weighted by the time spent there. Lung function was measured. Random effects linear model was used to analyze the relation between PEF and exposure.	In asthmatic children (aged 6-15 years), significant reduction of morning PEF was associated with PM. Significant reduction of PEF was also linked to NO_2 level. No effect was found in non-asthmatic children.	Quackenboss *et al.*, 1991
TSP (annual mean: in residential area = 389 $\mu g/m^3$; in suburban area = 261 $\mu g/m^3$; in industrial area = 449 $\mu g/m^3$)	The lung function of adults was measured in residential, suburban and industrial areas in Beijing, China, during August 1986. The concentrations of SO_2 and TSP were measured. Multiple linear regression techniques were used, and age, sex, education, passive smoking, pollutant levels, coal stove heating, and lung fuction were included.	A per-unit increase in ln TSP ($\mu g/m^3$) could result in a 131.4 ml reduction in $FEV_{1.0}$ and a 478.7 ml reduction in FVC. SO_2 and heating with coal were also associated with a reduced $FEV_{1.0}$ and FVC.	Xu *et al.*, 1991
PM_{10} (mean = 76 $\mu g/m^3$, range =	Symptomatic and asymptomatic school children of grades 5 and 6 were assessed for lung function	Relatively small but statistically significant negative associations between PEF and PM_{10}	Pope and Dockery, 1992

7-251 $\mu g/m^3$)	changes during the winter of 1990-1991, in Utah Valley. PM_{10}, SO_2, and H^+ were monitored. Single period and polynomial-distributed lag models were estimated by regressing ΔPEF on daily PM_{10} levels, low temperature, and a linear time trend variable. Weighted least-squares regression was used. Autocorrelation was corrected.	pollution were observed for both symptomatic and asymptomatic children. The association was strongest for the symptomatic sample. PEF changes were more close associated with 5-day moving-average PM_{10} levels than with concurrent-day levels. The association was also observed at PM_{10} levels below the 24-hr standard of 150 $\mu g/m^3$.	
PM_{10} (mean = 55 $\mu g/m^3$, range = 1-181 $\mu g/m^3$)	The relation between lung function and PM_{10} was assessed among smokers with mild to moderate COPD in Utah Valley. PM_{10} and daily low temperatures were monitored. Linear regression was used.	A small but statistically significant inverse association was observed between lung function (ΔFEV_1 and $\Delta FEV_1/FVC$) and changes in PM_{10}. An increase in 100 $\mu g/m^3$ of PM_{10} was associated with a marginal (2%) decline in FEV_1. The effect of PM_{10} was greater for men than for women. The effect was nearly the same for those with airway hyperresponsiveness versus those without.	Pope and Kanner, 1993
$PM_{2.5}$ (range = 5-45 $\mu g/m^3$)	Lung function was measured among elementary school children before, during and after two winter heating seasons, in Seattle area. $PM_{2.5}$ was monitored using a light-scattering instrument. Random effects	An increase in $PM_{2.5}$ levels was associated with decline in asthmatic children's lung function. FEV_1 and FVC in the asthmatic children dropped an average of 34 and 37 ml	Koenig *et al.*, 1993b

	linear regression was used to analyze the association between $PM_{2.5}$ levels and children's lung function.	respectively for each 20 $\mu g/m^3$ increase in $PM_{2.5}$.	
PM_{10} (6 days above 110 $\mu g/m^3$, 1 day above 150 $\mu g/m^3$)	A diary was used to record acute respiratory symptoms and medication use of children (6-12 years old) with chronic respiratory symptoms, in the winter of 1990-1991, in the Netherlands. PM_{10}, SO_2, NO_2, and black smoke were monitored. Multiple linear regression analysis was performed to evaluate the association between air pollution and morning and evening PEF. The concentrations of pollutants of the same day, the previous day and the average of the previous week were used separately as independent variables. Day of the week, ambient temperature, and day of study were included in the regression.	There were small but significant negative associations of PM_{10}, black smoke, and SO_2 with both morning and evening PEF.	Roemer *et al.*, 1993
PM_{10} (mean = 17.9-35.2 $\mu g/m^3$) $PM_{2.1}$ (mean = 5.8-20.7 $\mu g/m^3$) $SO_4^=$	Lung function was examined among white children aged 8-12 years from 22 communities in the U.S.A. and Canada. PM_{10}, $PM_{2.1}$, $SO_4^=$, H^+, SO_2, and O_3 were monitored. A two-stage logistic regression model was used. First, a city-specific adjusted means were calculated by regressing the natural logarium of the lung function measurements on sex, ln age, ln	Annual particle acidity was strongly correlated with $PM_{2.1}$ and $SO_4^=$. Children living in the community with the highest levels of PM_{10}, $PM_{2.1}$, $SO_4^=$, and H^+ were significantly more likely to have impaired FVC and FEV_1 compared to children living in the least polluted community.	Raizenne *et al.*, 1993

(mean = 6.8-77.3 $\mu g/m^3$)	height, ln weight, and an interaction of sex and ln height. The adjusted means were then regressed against the city-specific air pollution measurements. The prevalence of children whose lung function was ≤85% of predicted was calculated, and the logits were regressed against the city-specific pollutants. The logistic regression coefficients were expressed as odds ratios.		
PM_{10} (mean = 44.9 $\mu g/m^3$; range = 14.1-126.1 $\mu g/m^3$) $SO_4^=$ (mean = 6.7 $\mu g/m^3$; range = 0-29.7 $\mu g/m^3$)	Lung function was recorded from 7 to 11-year-old children during three consecutive winters in the Netherlands. PM_{10}, $SO_4^=$, NO_2, SO_2, nitrates, gaseous nitrous acid, and H^+ were monitored. Linear regression analysis was used. The number of days since study was included in the regression models to adjust for lung growth.	A weak negative association between the concentrations of PM_{10}, NO_2, $SO_4^=$, nitrate, nitrous acid, and lung function was found. H^+ level was low.	Hoek and Brunekreef, 1994
TSP (annual means = 85, 133 and 101 $\mu g/m^3$ for Lancaster, Glendora and Long Beach, respectively)	Lung function was examined among smokers and non-smokers in the Southern California air basin. Levels of TSP, $SO_4^=$, SO_2, NO_2, the oxidants were monitored. Subjects were divided into never-smokers, former smokers, quitters, and continuing smokers. One-way and two-way analysis of	For male residents, the mean decline in FEV_1 attributable to living in heavily polluted area was 23.6 ml/yr. The decline in FEV_1 attributable to smoking > 1pack of cigarettes per day was 33.3 ml/yr. In female non-smokers, but not consistently in female	Tashkin *et al.*, 1994

$SO_4^=$ (means = 4.5, 11.0 and 11.3 $\mu g/m^3$ for Lancaster, Glendora and Long Beach, respectively)	covariance were used after adjustment for age, height, FEV_1 at study entry, and a history of allergic disorders. Multiple regression analysis was used for current and former smokers.	smokers, residence in heavily polluted area was associated with a significantly greater annual decline in FEV_1.	
PM_{10} (mean = 17.9-35.2 $\mu g/m^3$) $PM_{2.1}$ (mean = 5.8-20.7 $\mu g/m^3$) $SO_4^=$ (mean = 6.8-77.3 $\mu g/m^3$)	Lung function was examined among white children aged 8-12 years from 22 communities in the U.S.A. and Canada. PM_{10}, $PM_{2.1}$, $SO_4^=$, H^+, SO_2, and O_3 were monitored. A two-stage logistic regression model was used. First, a city-specific adjusted means were calculated by regressing the natural logarium of the lung function measurements on sex, ln age, ln height, ln weight, and an interaction of sex and ln height. The adjusted means were then regressed against the city-specific air pollution measurements. The prevalence of children whose lung function was ≤85% of predicted was calculated, and the logits were regressed against the city-specific pollutants. The logistic regression coefficients were expressed as odds ratios.	Annual particle acidity was strongly correlated with $PM_{2.1}$ and $SO_4^=$. Children living in the community with the highest levels of PM_{10}, $PM_{2.1}$, $SO_4^=$, and H^+ were significantly more likely to have impaired FVC and FEV_1 compared to children living in the least polluted community.	Raizenne *et al.*, 1995
PM_{10}	Twice daily peak expiratory flow rate (PEFR)	A 12-hr exposure to a 125-nmol/m^3 increase in	Neas *et al.*, 1995

(12 hr mean = 35.6 μg/m^3; max. = 83.4 μg/m^3) $PM_{2.5}$ (12 hr mean = 24.5 μg/m^3; max. = 88.1 μg/m^3) Total $SO_4^=$ (12 hr mean = 147.0 nmol/m^3; max. = 515 nmol/m^3) Particle-strong acidity (12 hr mean = 102 nmol/m^3; max. = 676.4 nmol/m^3)	measurements during the summer of 1990 were reported in Uniontown, Pennsylvania. Daily SO_2, PM_{10}, $PM_{2.5}$, total $SO_4^=$, particle-strong acidity, ozone and temperature were measured. An autoregressive linear regression model was used. The covariates included a linear trend parameter, a binary indicator of whether the observation point was in the morning or evening, and the average temperature and pollutant concentration of a single pollutant for the 12-hr monitoring period.	total $SO_4^=$ was associated with a -2.8 l/min deviation in the group mean PEFR (95% CI -0.54 to -5.08). A 12-hr exposure to a 125 nmol/m^3 increment in particle-strong acidity was associated with a -2.5 l/min deviation in the group mean PEFR (95% CI -0.8 to -4.2). O_3 had similar effect.	
PM_{10} (mean = 6.6-10.7 μg/m^3) $SO_4^=$ (mean = 53.4-84.5 μg/m^3)	Lung function was studied among children participating in a summer camp in the Austrian Alps. PM_{10}, H^+, $SO_4^=$, O_3, ammonium ion components, and daily pollen counts were monitored. Linear regression analyses for repeated measurements were used. Models were also stratified by asthma medication and respiratory symptoms. The time trend of lung function measurements was analyzed by	A decrease in FEV_1 was associated with an increase in the levels of PM_{10} and H^+ (- 6.7 ml/μg/m^3 for PM_{10}, and -0.99 ml/nmol/m^3 for H^+). The decrease in FEV_1 was more pronounced when the mean exposure during the previous 3 days was considered (-16.54 ml/μg/m^3 for PM_{10}, and -3.07 ml/nmol/m^3 for H^+).	Studnicka *et al.*, 1995

	regression of the day of study on the daily mean FEV_1 and FVC.		

Table 3.1.5. Summaries of recently published controlled human clinical studies relating adverse health effects to particulate matter exposure

Exposure concentrations and particle size	Study Description	Results and Comments	References
Mouthpiece study: Hydroxymethnesulfonic acid (HMSA, 0-1000 μM) + H_2SO_4 (50 μM), or H_2SO_4 (50 μM alone); MMAD 6.1 μm. Chamber study: HMSA (1 mM) + H_2SO_4 (5 mM), or H_2SO_4 (5 mM alone); MMAD 7 μm.	HMSA is a bisulfite adduct of formaldehyde, a common constituent of California acid fogs. Mild to moderate asthmatics, 20 to 40 years old, were studied. Nine subjects performed mouthpiece inhalation for 3 min. In chamber study, 10 subjects inhaled acid aerosols for 1 hr while doing intermittent exercise. Lung function was measured. Specific airway resistance was analyzed.	Mouthpiece study did not show any significant changes in lung function by inhalation of H_2SO_4 or H_2SO_4 plus HMSA. In chamber study, acid exposures caused sight increases in respiratory symptoms. The increase caused by HMSA was not statistically different from that caused by H_2SO_4.	Aris *et al.*, 1990
H_2SO_4 46 or 127 μg/m^3; MMAD 0.5 μm.	Thirty two asthmatics (8-16 years old) were exposed to low and high concentrations of H_2SO_4 oronasally, for 30 min, while doing intermittent moderate exercise. A subgroup (21 subjects) were exposed to 134 μg/m^3 of H_2SO_4 with 100% oral breathing. Symptoms and lung function were recorded.	No symptomatic or lung function changes were observed with any treatments.	Avol *et al.*, 1990

HNO_3 0.5 mg/m^3, or H_2O fog, or air, followed by O_3 0.2 ppm; MMAD of aerosols 6 μm.	Healthy, athletic subjects were exposed to aerosols or air for 2 hr while doing exercise. After a 1-hr break, they exercised for 3 hr in an atmosphere containing 0.2 ppm of O_3. Lung function was measured.	No direct effects of acid aerosol exposure were observed. Exposure to acid aerosols did not potentiate O_3-induced decrements of lung function.	Aris *et al.*, 1991a
Mouthpiece study: H_2SO_4 or NaCl 3 mg/m^3; MMAD 6 or 0.4 μm. Chamber study: H_2SO_4 0.96-1.4 mg/m^3; MMAD 6 μm.	Asthmatics (23-37 years old) were exposed to H_2SO_4 as follows: (1) Mouthpiece: Subjects were exposed to H_2SO_4 (6 or 0.4 μm) for 16 min, at rest. (2) Mouthpiece: Subjects were exposed to H_2SO_4 (relative humidity 100%, 6 μm; relative humidity <10%, 0.3 μm), at rest or doing exercise. (3) Chamber: Subjects were exposed to H_2SO_4 for 1 hr, at water contents of 0.5 or 1.8 g/m^3 while doing intermittent exercise.	In study (1), no effect on specific airway resistance or symptom scores were found. In study (2), no effect of either high or low humidity and H_2SO_4 was found. In chamber study (3), no effect of different water contents and H_2SO_4 was seen on lung function or symptom scores.	Aris *et al.*, 1991b
H_2SO_4 (100 μg/m^3, MMAD 0.5 μm) Carbon black (200 μg/m^3, MMAD 0.5 μm) H_2SO_4-coated carbon (100 μg/m^3)	Normal and asthmatic subjects aged 18-45 years, were exposed particles for 1 hr, with intermittent heavy exercise. Subjects gargled citrus juice before exposure to suppress airway ammonia. Lung function and bronchial reactivity to methacholine were measured.	Group data showed no effects of any exposure on any health measure. One asthmatic subject showed clinical symptoms with excess airway constriction after exposed to H_2SO_4 coated carbon.	Anderson *et al.*, 1992

H_2SO_4 (1000 μg/m^3; MMAD 0.9 μm)	Healthy, non-smokers (20-39 years old) were exposed to aerosols for 2 hr, with intermittent exercise. Bronchial lavage was performed 18 hr later.	Exposure to H_2SO_4 did not change the numbers of polymorphonuclear leucocytes and T lymphocytes significantly. No significant change was seen in release of superoxide anion or in inactivation of influenza virus by macrophages *in vitro*. Antibody-mediated cytotoxicity of alveolar macrophages increased in association with H_2SO_4 exposure.	Frampton *et al.*, 1992
H_2SO_4 (35 or 70 μg/m^3; MMAD 0.6 μm)	Adolescent asthmatic subjects (13-18 years of age) were exposed to H_2SO_4 via a mouthpiece with nose clips in place for 45 or 90 min, while doing intermittent moderate exercise. Oral ammonia was measured. All subjects drank lemonade prior to and during exposure. Lung function was measured.	The 45 min, but not 90 min, exposures were associated with significant decreases in FEV_1 (-6% or -3% for 35 or 70 min, respectively). Changes in FVC or resistance were not significant.	Koenig *et al.*, 1992
H_2SO_4 (70 or 130 μg/m^3. At the mouthpiece, H_2SO_4 is at 51-176 μg/m^3). MMAD 0.72 μm	Young asthmatic subjects (12-19 years of age) were exposed to H_2SO_4 via a mouthpiece for 40 min including 10 min moderate exercise. In a separate experiment, subjects drank lemonade to reduce the oral ammonia before the 45 min exposure. Lung function and ammonia were measured.	FEV_1 and FVC were significantly reduced at 2-3 min post-exposure, but not 20 min after exposure. The slopes of the change in FEV_1, V_{max50} and V_{max75} versus H^+ concentrations were related to the subjects' response to the percentage decrease in FEV_1 after exercise challenge.	Hanley *et al.*, 1992
$(NH_4)_2SO_4$ (70 μg/m^3;	Healthy and asthmatic subjects aged 60-76 years,	Lung function parameters in either group did	Koenig *et al.*,

MMAD 0.6 μm); H_2SO_4 (74-82 μg/m^3; MMAD 0.6 μm)	were exposed to aerosols for 40 min including 10 min light exercise, via a mouthpiece. In a separate study, subjects drank lemonade before inhaling H_2SO_4. Oral ammonia levels and lung function were measured.	not show significant changes. After H_2SO_4 exposure, the changes in total respiratory resistance from baseline were significantly higher in asthmatic subjects (+16%) than in healthy subjects (-6%).	1993a
H_2SO_4 (500 μg/m^3; MMAD 10.9 μm)	Healthy subjects aged 20-31 years, were exposed to H_2SO_4 or saline fog for 40 min at rest and 20 min of exercise, in a head dome. The lung function, symptoms and responses to methacholine challenge were measured. The subjects inhaled technetium-99M radioaerosol (MMAD 3.4 μm) to detect the mocociliary clearance function of lower airways.	Symptoms, lung function and methacholine response were not affected by either fog. Tracheal clearance and outer zone clearance were more rapid after acid exposure than after saline exposure.	Laube *et al.*, 1993
O_3 (0.12 ppm) + NO_2 (0.3 ppm); O_3 (0.12 ppm) + NO_2 (0.3 ppm) + H_2SO_4 (68 μg/m^3); O_3 (0.12 ppm) + NO_2 (0.3 ppm) + HNO_3 (0.05 ppm). MMAD 0.6 μm.	Adolescent allergic asthmatic subjects (12-19 years old) were exposed to test atmospheres by mouthpiece for 90 min with intermittent exercise. Lung function was measured on both test day and on the third day. The responses to methacholine challenge was measured on the third day post-exposure.	There was no significant change in lung function after any exposure protocol. Some subjects left the study because of uncomfortable symptoms associated with the exposures to pollutants (6/28).	Koenig *et al.*, 1994

H_2SO_4 (100 $\mu g/m^3$); O_3 (0.12 ppm); $H_2SO_4 + O_3$; MMAD 0.5 μm.	Healthy and asthmatic subjects (18-50 years old) were exposed to aerosols in a chamber for 6.5 hr, with six 50-min exercise periods. Subjects drank lemonade before exposed to H_2SO_4. Lung function, bronchial reactivity to methacholine, and symptoms were measured.	Exposure to H_2SO_4 alone caused no significant changes in lung function, symptoms or bronchial reactivity. Exposure to O_3 alone or $O_3 + H_2SO_4$ caused significant decline in FEV_1, smaller on the second day than on the first day. Bronchial reactivity increased significantly after exposure to O_3 with or without H_2SO_4. Marginally greater changes in lung function and bronchial reactivity were seen with $O_3 + H_2SO_4$ than with O_3 alone.	Linn *et al.*, 1994
Bagged polluted air, TSP (202 $\mu g/m^3$); SO_2 (112 ppb); NO_2 (488 ppb); CO (3.4 ppm)	Healthy and asthmatic subjects (23-48 years old) were exposed to bagged polluted air via a mouthpiece for 30 min. Lung function and bronchial reactivity to methacholine challenge were measured.	For normal subjects, no differences in lung function and bronchial reactivity were noted after exposure to polluted air. For asthmatics, significant decreases in FEV_1 and FEV_1/FVC, and increases in airway reactivity and baseline resistance values, occurred after the exposure to polluted air.	Yang and Yang, 1994
H_2SO_4 (100 $\mu g/m^3$) or saline, followed by O_3 (0.08, 0.12, or 0.18 ppm)	Healthy and allergic asthmatic subjects (18-45 years old) were exposed to H_2SO_4 or saline aerosols for 3 hr. On the next day, subjects were exposed to O_3 for 3 hr. Lung function was measured 2 and 4 hr after	For the healthy subjects, no changes in symptoms or lung function were seen after exposure to either aerosols or ozone. No aerosol-O_3 interaction was found. For the	Utell *et al.*, 1994

	exposure on the O_3 days.	asthmatic subjects, Preexposure to H_2SO_4 had no direct effect on lung function but appeared to enhance the small mean decrements in FVC that occurred in response to 0.18 ppm O_3 (-6.8%). Individual response in asthmatics was variable. There was interaction of H_2SO_4 and O_3 on lung function both immediately and 4 hr after exposure.	
H_2SO_4 (90 ± 10 $\mu g/m^3$) or NaCl (100 $\mu g/m^3$)	Seventeen asthma (age 20-57 years) and 17 COPD patients (age 52-70 years) were exposed to H_2SO_4 or NaCl for 2 hr with intermittent exercise. Lung function was measured before and after exposure.	In subjects with COPD, exposure to NaCl or H_2SO_4 aerosols did not cause a significant decrease in FVC, FEV_1 or SG_{aw} from baseline. In asthmatic subjects, mild decrease in FEV_1 and SG_{aw} from baseline was found after H_2SO_4 exposure.	Morrow *et al.*, 1994

Table 3.2.1. Summaries of recently published epidemiological studies relating human mortality and morbidity to ambient SO_2 levels

SO_2 concentrations	Study Description	Results and Comments	References
mean of the hourly max.: May - October =13.7 - 16.1 ppb; November - April = 12.0 - 16.4 ppb)	Attendances at the emergency departments of 9 acute care hospitals in Vancouver region from July 1, 1984 to October 31, 1986, were recorded. Daily temperature, SO_2, NO_2, $SO_4^=$, COH and ozone were mornitored. Pearson correlation coefficients were calculated between asthma visits and pollution variables on the same day and lagged 24 and 48 hr, separately for the periods May-October, and November-April.	In summer, in 15-60 age group, asthma and respiratory visits were correlated with SO_2 and $SO_4^=$ levels on the same day or lagged 24 hr. In winter, in all age groups, all respiratory visits but not asthma alone, were correlated with SO_2 levels on the same day, and lagged 24 and 48 hr. In the $\geq$60 yr age group in winter, SO_2 levels were correlated to asthma.	Bates *et al.*, 1990
annual mean: in residential area = 128 $\mu g/m^3$; in suburban area = 18 $\mu g/m^3$; in industrial area = 57 $\mu g/m^3$)	The lung function of adults was measured in residential, suburban and industrial areas in Beijing, China, during August 1986. The concentrations of SO_2 and TSP were measured. Multiple linear regression techniques were used, and age, sex, education, passive smoking, pollutant levels, coal stove heating, and lung fuction were included.	A per-unit increase in ln SO_2 ($\mu g/m^3$) could result in a 35.6 ml reduction in $FEV_{1.0}$ and a 142.2 ml reduction in FVC. TSP and heating with coal were also associated with a reduced $FEV_{1.0}$ and FVC.	Xu *et al.*, 1991
Yearly mean = 9-19 ppb; standard	Shumway *et al.* 's 1970-1979 Los Angeles mortality dataset was analyzed using a high-pass filter to allow	There was no significant associations between short-term variations in total mortality and SO_2	Kinney and Ozkaynak,

deviation = 4-6 ppb.	investigation of short-wave (acute) associations with environmental variables (by removing seasonality effects). Environmental variables were considered in regression analyses included temperature, relative humidity, extinction coefficient, KM, SO_2, NO_2, CO and O_3.	concentrations, after controlling for temperature. Day-of-week effects were found not to affect the relationships. The results demonstrated significant mortality associations with O_3 lagged 1 day, and with temperature, NO_2, CO and KM.	1991
Yearly 24-hr mean = 56.5 ± 22.5 $\mu g/m^3$, range = 17-160 $\mu g/m^3$; yearly 1-hr mean for max. = 141.9 $\mu g/m^3$, range = 14-720 $\mu g/m^3$.	Emergency room admissions for chronic obstructive pulmonary disease (COPD) in Barcelona, Spain, during 1985-1986, were assessed. Black smoke, SO_2, CO, NO_2, and O_3 were measured. Autocorrelation was controlled by transfer function modelling for 2-day lag minimum temperature, season, day of week and 1-day lag wind velocity. Autoregressive linear regression analysis was used.	SO_2, black smoke, CO, and NO_2 were intercorrelated. After adjusting for meteorologic and temporal variables, daily emergency room admissions for chronic obstructive pulmonary disease increased by 0.02 and 0.01 for 1 $\mu g/m^3$ of SO_2 and black smoke, respectively, and 0.11 for 1 mg/m^3 of CO.	Sunyer *et al.*, 1991
Yearly 24-hr mean = 21.0 ppb; 5% to 95% tiles = 6 to 46 ppb)	Total- and cause-specific daily mortality in Philadelphia, PA during 1973-1980 was related to daily TSP and SO_2 (n = 2,700 days). No other pollutants were considered in the analysis. Poisson regression models, using GEE methods, included controls for year, season, temperature, and humidity. Autocorrelation was addressed via autoregressive terms in model.	Strongest associations were found with pollution on the same and prior days. SO_2 associations were non-significant in simultaneous models with TSP, but correlations of their coefficients were not reported.	Schwartz and Dockery 1992a

Daily mean 5% to 95% tiles in winter = 103-1206 μg/m3, in summer = 20-376 μg/m3, all season = 27-952 μg/m3; daily maxi. 5% to 95% tiles in winter = 200-2700 μg/m3, in summer = 40-840 μg/m3, all season = 60-2200 μg/m3.	Daily total mortality in Erfurt, East Germany, during 1980-1989 (median = 6/day) was related to SO_2, SP, temperature, relative humidity, and precipitation. SP measurements were made only 1988-1989. Autoregressive Poisson models employed (due to low deaths/day) also included indicator variables for extreme temperatures and adjustments for trend, season, and influenza epidemics.	Both SO_2 and SP were found to be significantly associated with increased mortality. In a simultaneous regression, SP remained significant while SO_2 did not. Correlations of these coefficients were not provided, however. Pollution effect size was similar to that for meteorology.	Spix *et al.*, 1993
Daily mean = 10.0 μg/m^3, range = 0-56 μg/m^3; daily max. = 31.0 μg/m^3, range = 1-241 μg/m^3	Daily attendances for asthma attacks at the emergency room of Oulu University Central Hospital were recorded during 1985-1986, together with daily temperature, humidity, barometric pressure, rainfall, NO_2, SO_2, H_2S, TSP, and pollen counts. Pearson's correlation coefficient and partial correlations were calculated. The stepwise discriminant analysis and multiple regression analysis were used.	Significant correlations were found between asthma visits and the levels of NO_2, SO_2, TSP, and H_2S. Intercorrelations were found between pollutants and temperature. Only NO_2 correlated significantly with attendances after standardisation for temperature.	Rossi *et al.*, 1993

Mean = 102.3 $\mu g/m^3$; 5% to 95% tiles = 6-391 $\mu g/m^3$.	Daily deaths during 1989 in two residential areas in Beijing, China, (mean total = 21.6/day) was related to TSP and SO_2 using Poisson methods. Controlling indicator variables for quintiles of temperature and humidity, as well as for Sunday also were included. Long-wave confounding and autocorrelation were not directly addressed. However, season-specific results presented.	Significant mortality associations were found for ln (SO_2) and ln (TSP). Associations were strongest for chronic respiratory diseases. In simultaneous regressions, SO_2 was significant, but not TSP. However, the two pollutants were highly correlated with each other (r = 0.6), as well as with temperature. In season-specific analyses, both pollutants were significant in summer, but only SO_2 in winter.	Xu *et al.*, 1994
Maximal 24-hr level = 81.9 ppb; 10% to 90% tiles = 0.8-17.9 ppb.	A daily diary of upper and lower respiratory symptoms was collected from the parents of school children in six U.S. cities, between April and August, 1984-1985. PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, $SO_4^=$, and H^+ were monitored. Autoregressive logistic regression using GEE was applied.	A 10 ppb increment in 24-h SO_2 concentration was associated with a relative odds of 1.28 (95% CI 1.13-1.46) for the incidence of lower respiratory symptoms, and a relative odds of 1.15 (95% CI 1.02-1.31) for the incidence of coughing, after controlling for temperature, city, and day of the week. Significant associations were also found between PM_{10} or $PM_{2.5}$ and incidence of coughign, and upper and lower respiratory symptoms.	Schwartz *et al.*, 1994
Daily mean = 19 $\mu g/m^3$ (6.7 ppb); range = 0.2-95	The relation between hospital admissions for chronic respiratory diseases and low-level air pollution in 1987-1989 was studied in Helsinki. SO_2, NO_2, O_3	The effect of SO_2 was observed only among those $\leq$65 yr. RR for admissions for 2.7-fold increase of SO_2 concentration on the same day was 1.31	Ponka and Virtanen, 1994

$\mu g/m^3$ (0.1-33 ppb).	and TSP were monitored. The relation was analyzed using Poisson regressions controlled for weather, season, time trends, and day of the week.	(95% CI 1.01-1.70). RR for admissions for 2.7-fold increase of SO_2 concentration after a 3-day lag was 1.39 (95% CI 1.05-1.86).	
Yearly mean = 39.06 $\mu g/m^3$, 10% to 90% tiles = 24-62 $\mu g/m^3$; summer mean = 37.77 $\mu g/m^3$; spring mena = 42.87 $\mu g/m^3$; autumn mean = 40.91 $\mu g/m^3$; winter mean = 34.18 $\mu g/m^3$.	Hospital admissions for asthma and acute respiratory diseases between 1988-1990 were studied in Birmingham, UK. Smoke and SO_2 levels were monitored. Data were divided into seasons, and the relations between hospital admissions and pollutnat levels were analyzed by stepwise least squares regression models. Temperature, pressure, and humidity were entered into the model if they showed significant association with hospital admissions.	Significant associations were found between hospital admissions for respiratory diseases lagged by 2 days, and smoke and SO_2 levels in winter. Asthma admissions were also significantly associated with smoke and SO_2 levels lagged by 2 days in winter. In winter, a 100 $\mu g/m^3$ rise in SO_2 might result in 4 (95% CI 0-7) mor asthma adimssions and 15.5 (95% CI 6-25) more respiratory admissions each day.	Walters *et al.*, 1994
12 hr mean = 10.2 ppb; max. = 44.9 ppb	The daily presence of cold, cough, or wheeze symptoms and lung function changes of children during the summer of 1990 were recorded in Uniontown, Pennsylvania. Daily SO_2, PM_{10}, $PM_{2.5}$, total $SO_4^=$, particle-strong acidity, ozone and temperature were measured. An autoregressive logistic regression model was used. The covariates	A 12-hr exposure to a 10 ppb increase in SO_2 was associated with increased cough incidence (OR = 1.53, 95% CI 1.07-2.2), and with decrements of lung peak expiratory folw rate (-1.25 liters/min, 95% CI -2.75 to 0.25). PM and O_3 had similar effect.	Neas *et al.*, 1995

	included a linear trend parameter, a binary indicator of whether the observation point was in the morning or evening, and the average temperature and pollutant concentration of a single pollutant for the 12-hr monitoring period preceding the diary report with separate pollutant effect estimates for daytime and overnight exposures.		
Mean = 4.7 ppb; 95% tile = 17 ppb.	Hospital admissions for respiratory diseases during April 1, 1981 to December 31, 1991, were investigated for 16 cities across Canada. Daily ozone, SO_2, NO_2, CO, and soiling index (COH) were recorded. COH is correlated with airborne particles. The multivariate random effects relative risk regression model was used to relate the environmental variables to the daily respiratory admissions. A 19-day weighted moving regression filter was employed to remove seasonal patterns from the data.	All the environmental variables were positively associated with respiratory hospitalizations.	Burnett *et al.*, 1995
Mean in New Haven = 78 $\mu g/m^3$ (29.8 ppb); 10% to 90% tiles = 23-159 $\mu g/m^3$,	Daily counts of hospital admissions for respiratory diseases were constructed for persons aged ≥65 years in New Haven, Connecticut, and Tacoma, Washington, during January 1, 1988 to December 31, 1990. Daily SO_2, PM_{10} and ozone were monitored.	In one pollutant model, RR for a 50 $\mu g/m^3$ increase of SO_2 levels in New Haven was 1.03 (95% CI 1.00-1.13); in Tacoma RR was 1.06 (95% CI 1.01-1.12). The SO_2 association with respiratory hospital admissions of the elderly was	Schwartz, 1995

8.8-60.7 ppb). Mean in Tacoma = 44 $\mu g/m^3$ (16.8 ppb); 10% to 90% tiles = 18-74 $\mu g/m^3$, 5.7-28.2 ppb).	Daily respiratory admission counts were regressed on temperature, humidity, day of the week, and air pollutants. A 19 day weighted moving regression filter was used to remove all seasonal and subseasonal patterns from the data. Each pollutant was first examined individually and then multiple pollutant models were fitted.	substantially attenuated by control for O_3 in both cities, and by control for PM_{10} in Tacoma. The PM_{10} associations were little changed by controlling for ozone or SO_2. Levels of O_3 were also associated with respiratory admission independently.	
Daily mean = 117 $\mu g/m^3$	Adult patients with diagnoses of asthma or COPD were studied for a period of 4 weeks during which they kept records of their peak expiratory flow (PEF) rates, symptoms and bronchodilator use. Ambient SO_2, O_3 and NO_2 were measured. Multiple regression analysis was used.	There were modest but significant increases in PEF variability, bronchodilator use, and wheeze with increasing SO_2 levels. Patients in whom the provocative dose of methacholine causing a 20% fall in FEV_1 was below 12.25 µmol were refered to as reactors, and were more sensitive to the increases in SO_2 concentrations.	Higgins *et al.*, 1995
Mean = 42.6 $\mu g/m^3$, min. = 7.0 $\mu g/m^3$, max. = 87.7 $\mu g/m^3$	This is a cross-sectional study. Data on respiratory symptoms were available on 11,552 members of the 1958 national birth cohort. Counties in the UK were ranked by annual average levels of black smoke and SO_2, and then divided into five groups. The subject's county of residence determined their categorisation of pollution exposure. Logistic regression was used, adjusting for social class, sex, and smoking.	No symptoms were associated with SO_2. Phlegm symptoms increased with increasing black smoke levels with evidence of a plateau.	Scarlett *et al.*, 1995

No exact number reported in the paper.	Data on hospital admissions for acute respiratory conditions during 1988-1990 were obtained by electoral ward from the West Midlands, UK. Data on black smoke, NO_2 and SO_2 were collected. Indirect age-sex standardised hospitalisation rates (SHR) for all respiratory conditions and asthma were calculated. Multivariate regression models were used to assess the relationship between individual pollutants and the SHR. The Townsend score and percentage of the population from non-white ethnic groups were included in all models to adjust for ethnicity and socioeconomic deprivation.	SO_2 and black smoke were not associated with hospital admissions. NO_2 was associated with hospital admission rates for all ages.	Walters *et al.*, 1995
Daily mean = 70 ppb; range = 10-490 ppb.	Emergency visits for childhood asthma during the first 6 months of 1990 were investigated in Mexico City. Data on SO_2, O_3, NO_2, TSP and temperature were collected. Partial correlation and Poisson regression models were used, and day of the week, seasons, age, sex, pollutants and emergency visits were included. No autocorrelation was found.	The levels of O_3 and SO_2 were significantly associated with the number of emergency visits for asthma. The multivariate regression showed that the effect of SO_2 was substantially reduced when O_3 and other potential confounders were included in the model.	Romieu *et al.*, 1995
Spring mean = 16.8 ppb, min. to max. = 0.3 -	Daily total mortality in Philadelphia during 1973-1988 was investigated, and related to TSP, SO_2, ozone. Poisson regression and nonparametric	When all three pollution covariates and weather were considered simultaneously in the regression model, SO_2 was associated with mortality in	Moolgavkar *et al.*, 1995a

101ppb; summer mean = 15.7 ppb, min. to max. = 0.4 - 156 ppb; fall mean = 17.8 ppb, min. to max. = 0.7 - 100.4 ppb; winter mean = 25.4 ppb, min. to max. = 5.4 - 102.8 ppb	bootstrap and bias-corrected accelerated bootstrap confidence intervals were used. Both methods yielded similar results. The effects of weather were controlled by analyzing mortality separately for each season and including both pollution variables and quintiles of temperature in the regression models simultaneously.	spring (RR1.19, 95% CI = 1.06-1.33), fall (RR = 1.14, 95% CI = 1.00-1.29) and winter (RR = 1.21, 95% CI = 1.09-1.35), while Ozone was associated with mortality in summer (RR = 1.15, 95% CI = 1.07-1.24). TSP was not significantly associated with mortality in any season. The pollutant covariates were highly correlated.	
Mean = 16.98 ppb; standard deviation = 11.87 ppn; 5% to 95% tiles = 4.10-39.46 ppb.	Age and cause-specific daily mortality in Philadelphia, PA during 1973 and 1990 was related to daily TSP, SO_2, and O_3. Other environmental variables included were: temperature, barometric pressure, humidity, and precipitation. Various models were employed, including Poisson and autoregressive. Prefiltering methods also were applied to remove long-waves in data.	When all three pollutants were in the model, the significance of ozone was stronger than that of SO_2, and the significance of SO_2 was stronger than that of TSP. SO_2 effects were found in summer and fall for people $\leq$65 yr, and only in winter season for people $\geq$65 yr. SO_2 levels were associated with dealth due to cancer, cardiovascular diseases and pneumonia.	Li and Roth, 1995

4. Review of Indirect Health Effects

Potential indirect health effects of acid rain were reviewed in the 1990 Canadian Long-Range Transports and acid deposition assessment report (Toxic Air Pollution-Health Effects Section, 1990). The review reached the following conclusions:

(1) The acid deposition, and acidification of water supplies and soil result in subsequent mobilization of heavy metals, which may increase exposure to these metals through drinking water and food. Unregulated water supplies are not pH neutralized before distribution and increased acidification of the water can result in corrosion of the distribution system. The corrosion of metal plumbing systems can result in increased levels of potentially toxic heavy metals in the water.

(2) Of significant interest are cadmium, mercury, lead, arsenic, aluminum and chromium. Cadmium and mercury may enter into food chain to humans. Very low doses of lead can have subtle effects on the central nervous system that are observed as peripheral nerve dysfunction in adults or neurobehaviourial and developmental effects in children.

(3) Shallow wells may be especially susceptible to increases in metal concentrations and drilled bedrock wells may not be immune as heavy metals, like arsenic, may be mobilized from mineral sources into aquifers.

(4) In Ontario, elevated levels of dissolved copper, lead, and cadmium have been observed in water that was left undisturbed in distribution systems drawing water from privately supplied lake water. Northern Ontario, southwestern Ontario, the north shore of the St. Lawrence River in Quebec and areas of New Brunswick and Nova Scotia are areas in Canada that are very sensitive to acidification. An estimated 300,000 people in these areas obtain their drinking water from unregulated sources that may be affected by acid deposition.

(5) Flushing of the systems for five minutes reduced the concentrations of these untreated water systems.

In addition, the pollution of ambient particulate matter may cause visibility reduction, changes in climate, and damage to vegetation, which also indirectly affect the well-being of the entire human species.

4.1 Changes in visibility and climate

The term visibility implies that an object can be seen by an observer. Visibility reduction can be attributed to natural hazes formed from volcanic emissions or forest fire, or anthropogenic activities. Visibility reduction associated with anthropogenic activities is due primarily to light scattering by particles and to a lesser extent to absorption of light by atmospheric gases such as NO_2. Fine particles (i.e., those particles of diameter less than 1 to 3 μm) usually dominate light scattering. Particles smaller than 0.1 μm, though sometimes present in high numbers, are individually very inefficient at scattering light and thus contribute very little to visibility loss; particles larger than about 1 to 3 μm, though individually efficient at scattering light, usually exist in relatively small numbers and contribute only a small fraction of visibility loss.

Particle-induced visibility reduction may affect climate by reducing solar radiation at ground level, making less energy available for photosynthesis. Reduced solar radiation may alter local or regional temperatures. Furthermore, increased cloud formation may alter precipitation patterns.

4.2 Acidic deposition

Acidic deposition is the combined total of wet and dry deposition, with wet acidic deposition being commonly referred to as acid rain.

Land, vegetation, and bodies of water are the surfaces on which acidic deposition

accumulates. The ability of soils to tolerate acidic deposition depends on the alkalinity of the soil. Much of the eastern Canada is covered with thin soils with a relatively limited neutralizing capacity. In watersheds with this type of soil, lakes and streams are susceptible to low pH, resulting in the depletion of fishery resources.

A second area of concern is reduced tree growth in forests by acidic deposition, by preventing nutrients from being uptaken and by directly damaging leaves.

Acidic deposition also contributes to deterioration of building surface, and to damage to fabrics and other materials.

As discussed in the 1990 assessment report (Toxic Air Pollution-Health Effects Section, 1990), the major concern for acidic deposition lies in the increased exposure to heavy metals through drinking water and food. The acidification of soil may leach metals into surface waters, resulting in subsequent enhancement of heavy metals. Furthermore, unregulated water supplies are not pH neutralized before distribution, and increased acidification of the water can cause corrosion of the metal plumbing distribution systems, resulting in increased levels of potentially toxic heavy metals in the water.

In addition to cadmium, mercury, lead, arsenic, aluminum and chromium that have been discussed in the 1990 assessment report (Toxic Air Pollution-Health Effects Section, 1990), selenium has drawn an increasing interest as an important metalloid with industrial, environmental, biological and toxicological significance. Elevated concentrations of selenium in water samples in the United States have been noted at levels higher than U.S. EPA standard (10 ppb), which is associated with corrosion of household plumbing by soft, acidic water (Fishbein, 1991). Acute and chronic selenium toxicity has been observed in livestock and laboratory animals, involving various degrees of damage to internal organs, vascular edema, and hemorrhage (Fishbein, 1991). The signs of acute toxicity in farm and experimental animals most commonly mentioned in the literature are garlic odour of the breath, dyspnea, pulmonary edema, tachycardia, emesis, diarrhea, depression, ataxia, incoordination, paralysis and excessive salivation. Chronic exposure to elevated selenium in

food or drinking water causes reduced growth rate, decreased blood haemoglobin and liver toxicity. Human chronic toxicity of selenium has been reported, attributed to the increased selenium through consumption of food (Fishbein, 1991). The signs include bad teeth, skin disorder, gastrointestinal disturbances, garlic odour of the breath, and abnormalities of the nervous system including numbness, convulsions and paralysis.

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